Caso clinico

SAPIENZA
UNIVERSITÀ DI ROMA

Dipartimento di Sanità Pubblica e Malattie Infettive

Anamnesi

- 46 aa
- Professione: cardiologo
- Non fumatore, consumo sporadico di alcol
- Malattia reumatica in età infantile
- Tachicardia sinusale in situazioni di stress→atenololo
- Ipertensione arteriosa
- Storia di nefrolitiasi, accesso al DEA 1 mese fa per colica renale

Anamnesi

Da 10 gg

- Febbre (cuspidi 40° C)
- Dolore lombare riferito a coliche renali

Assumeva Azitromicina con scarso beneficio

Si recava pertanto al DEA…

19:57

- Pz in CGD, orientato, S/T, Giordano +
- PV nella norma
- ECG nella norma

- Urinocoltura
- Emocromo /ematochimici:

Hb	14 g/dL
GB	**13 540 cell/mmc** (N 88%, L 6%)
PLT	133 000 cell/mmc
PCR	**25.97 mg/dL**
Na+	137 mmol/L
K+	3.29 mmol/L
Cl-	98 mmol/L
APTT-ratio	0.87
PT-INR	1.37

Terapia somministrata:

SF
Paracetamolo a/b
SG
Ciprofloxacina
Esomeprazolo
Ketoprofene
Spasmex a/b

21:58

Subentra stato confusionale: “Pz soporoso, risvegliabile, disorientato s/t, E.O. neurologico nella norma”

TC cranio in urgenza

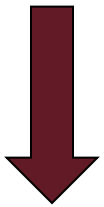
TC cranio

“Esame eseguito in regime di urgenza senza somministrazione di Mdc. **Focolaio emorragico intraparenchimale di circa 10 mm in sede occipitale sn, a localizzazione corticale-sottocorticale.** Non dilatazione del sistema ventricolare né degli spazi subaracnoidei. In asse strutture della linea mediana”

- SF
- Ketoprofene
- Ranitidina
- **Desametasone**
- **Mannitolo 18%**

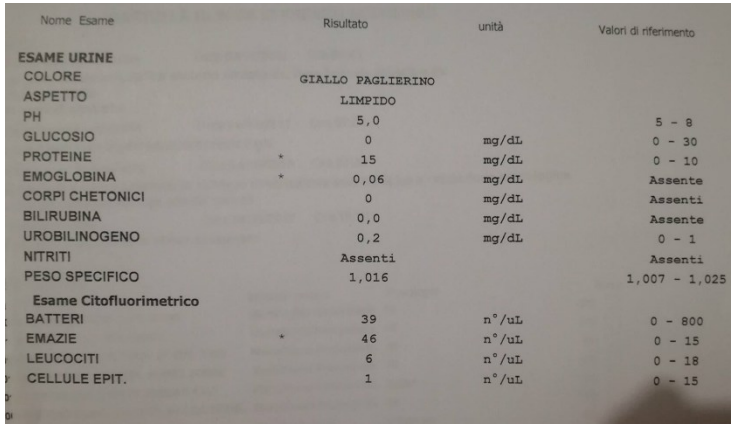
23:50

- EO: “CGD, rima buccale deviata a dx, deficit arto superiore dx, afasia globale”
- PV nella norma



- Emocromo/ematochimici
- Emocolture
- ECG
- EGA
- TC cranio
- ETT

EMOCROMO/EMATICI	
Hb	13.3 g/dL
GB	**24 240 cell/mmc** (N 88%, L 6%)
PLT	143 000 cell/mmc
PCR	**30.30 mg/dL**
Na+	134 mmol/L
K+	3.9 mmol/L
PT-INR	1.15



Nome Esame		Risultato	unità	Valori di riferimento
ESAME URINE				
COLORE		GIALLO PAGLIERINO		
ASPETTO		LIMPIDO		
PH		5,0		5 - 8
GLUCOSIO		0	mg/dL	0 - 30
PROTEINE	*	15	mg/dL	0 - 10
EMOGLOBINA	*	0,06	mg/dL	Assente
CORPI CHETONICI		0	mg/dL	Assenti
BILIRUBINA		0,0	mg/dL	Assente
UROBILINOGENO		0,2	mg/dL	0 - 1
NITRITI		Assenti		Assenti
PESO SPECIFICO		1,016		1,007 - 1,025
Esame Citofluorimetrico				
BATTERI		39	n°/uL	0 - 800
EMAZIE	*	46	n°/uL	0 - 15
LEUCOCITI		6	n°/uL	0 - 18
CELLULE EPIT.		1	n°/uL	0 - 15

EMOCOLTURE

Positive per Stafilococco aureus MRSA (FilmArray)

TC cranio

Presenza di petecchia emorragica di 10 mm in sede occipitale sinista para-falcale. Sistema ventricolare normo-conformato ed in asse.

Diagn Microbiol Infect Dis. 2012 Dec;74(4):349-55. doi: 10.1016/j.diagmicrobio.2012.08.013. Epub 2012 Sep 19.

Rapid identification of pathogens from positive blood cultures by multiplex polymerase chain reaction using the FilmArray system.

Blaschke AJ[1], Heyrend C, Byington CL, Fisher MA, Barker E, Garrone NF, Thatcher SA, Pavia AT, Barney T, Alger GD, Daly JA, Ririe KM, Ota I, Poritz MA.

Despite the increased knowledge in pathogenesis of microbial diseases and effective treatment, bloodstream infections (BSIs) remain a leading cause of death and high health care-related costs worldwide (1, 2). Appropriate antimicrobial therapy significantly lowers the mortality rate for patients with BSI (3). Initial antimicrobial treatment often includes the use of a broad spectrum of antibiotics, a strategy often used due to the lack of specific identification of the causative infectious agent. Conventional microbiological methods for identification of microorganisms from blood cultures, such as agar-based culture techniques, take a considerable time, from 12 to 72 h. In response, several microbiological methods for rapid and specific identification of infectious agents from positive blood culture bottles have been suggested, including pathogen-specific real-time PCR (4), fluorescence *in situ* hybridization using peptide nucleic acid probes (PNA-FISH) (5), PCR coupled to high-resolution melting curve analysis (6), and direct matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (7, 8). These methods are, however, relatively labor-intensive and in some instances have a narrow diagnostic spectrum. Moreover, none of them has the capacity to evaluate important antimicrobial susceptibility markers, including *mecA*, *vanA*, and *vanB*. There is a need for reliable, simple, and direct identification methods with short hands-on time involving limited expertise. BioFire Diagnostic's FilmArray system (FA; BioFire, Salt Lake City, UT) is a PCR-based platform developed and tested for the diagnosis of several infectious agents involved in different diseases, including respiratory viruses, *Bacillus anthracis*, *Francisella tularensis*, and *Yersinia pestis* (9–11). Recently, the FilmArray blood culture ID (FA BCID) panel was introduced (12). This panel was later improved, and the current panel includes 27 targets (Table 1). The FA BCID uses high-order multiplex PCR analysis to identify a number of pathogens and susceptibility markers directly from positive blood culture bottles in 1 h. The aims of the present study were (i) to analyze the performance of the FA BCID panel in prospective clinical samples and (ii) to analyze the effect of different parameters, including blood culture bottle type, time to detection in blood culture bottles, and reproducibility of results after long-term storage.

Category	Target
Gram-negative bacteria	*Enterobacteriaceae*
	Escherichia coli
	Enterobacter cloacae complex
	Klebsiella oxytoca
	Klebsiella pneumoniae
	Serratia marcescens
	Proteus spp.
	Acinetobacter baumannii
	Haemophilus influenzae
	Neisseria meningitidis
	Pseudomonas aeruginosa
Gram-positive bacteria	*Staphylococcus* spp.
	Staphylococcus aureus
	Streptococcus spp.
	Streptococcus agalactiae
	Streptococcus pyogenes
	Streptococcus pneumoniae
	Enterococcus spp.
	Listeria monocytogenes
Fungi	*Candida albicans*
	Candida glabrata
	Candida krusei
	Candida parapsilosis
	Candida tropicalis
Antibiotic resistance markers	*mecA*
	vanA/vanB
	KPC

ETT/EOT

TTE

"mitrale ispessita, con normali escursioni dei lembi; insufficienza di grado lieve. Valvola aortica ispessita, con normali escursioni dei lembi; insufficienza di grado lieve. **Non visualizzabili grossolane formazioni vegetanti**"

TEE

"…a livello aortico formazione filiforme ed allungata originante dalla cuspide coronarica sinistra, di 24 mm, molto mobile, di tenue consistenza, compatibile con lesione vegetante batterica, insufficienza valvolare con jet eccentrico proveniente da tutta la commissura superiore sn **di grado medio-severo"**

Risultati emocolture….

BATTERIOLOGIA

EMOCOL AEROB DA VENA PERIF. **POSITIVA**

Germe Identificato:

Microorganismo # 1 Staphylococcus aureus (STAAUR)

Tempo di positiviz

	1 STAAUR			
	SIR	MIC	SIR	MIC
Acido Fusidico	S	<=0,5		
Cefoxitina screening	-	Neg		
Clindamicina	S	0,25		
Daptomicina	S	1		
Eritromicina	S	1		
Gentamicina	S	<=0,5		
Levofloxacina	S	0,25		
Linezolid	S	4		
Oxacillina MIC				
Penicillina G				
R inducibile a Clindamicina				
Rifampicina				
Teicoplanina	S	<=0,5		
Tetraciclina	R	>=16		
Tigeciclina	S	0,25		
Trimetoprim/Sulfam.	S	<=10		
Vancomicina	S	1		

MSSA

Oxacillina

5 h dopo…

- Persiste deficit motorio, rima buccale deviata a dx
- PA 90/60
- Soporoso, risvegliabile agli stimoli verbali

Si richiede TC cranio di controllo

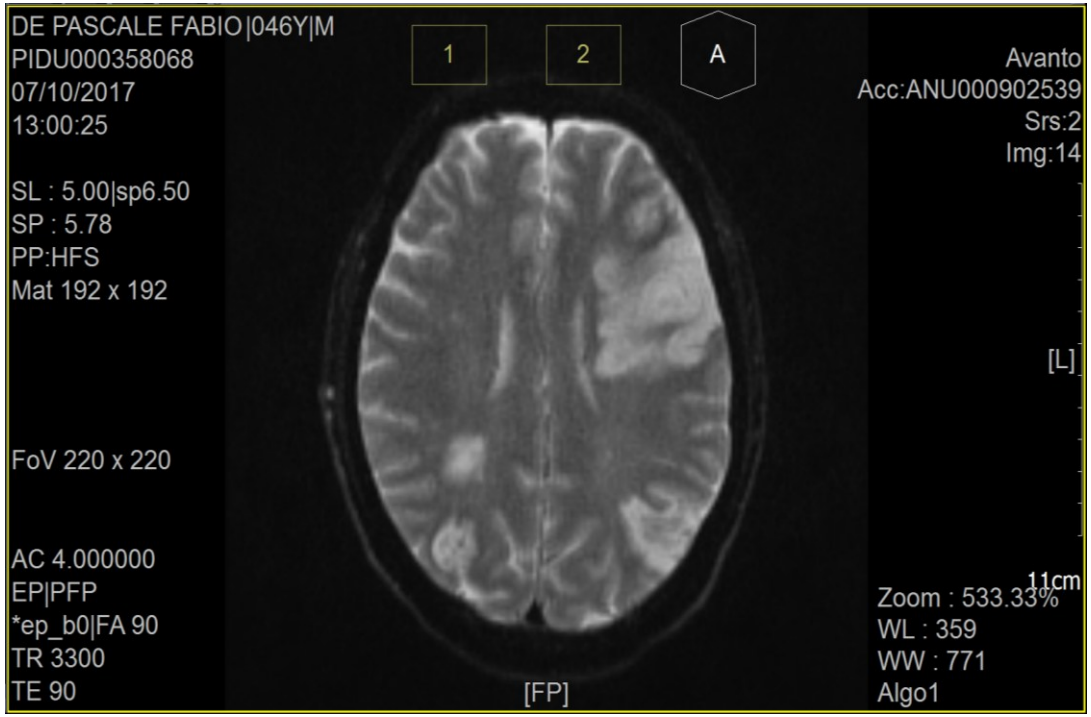
TC cranio

“voluminosa area ipodensa nel territorio di irrorazione della arteria cerebrale media di sn, da riferire a ischemia. Invariata la petecchia emorragica precendetemente segnalata in sede occipitale sn”

Consulenza cardiochirurgica

Non indicazioni ad intervento cardiochirurgico urgente, per alto rischio emorragico. Si consiglia RM.

In summary, symptomatic neurological events develop in 15–30% of all patients with IE and additional silent events are frequent. Stroke (ischaemic and haemorrhagic) is associated with excess mortality. Rapid diagnosis and initiation of appropriate antibiotics are of major importance to prevent a first or recurrent neurological complication. After a first neurological event, cardiac surgery, if indicated, is generally not contraindicated, except when extensive brain damage or intracranial haemorrhage is present.



RM encefalo

Multiple aree di restrizione della DWI, riferibili a lesioni vascolari ischemiche recenti, su base emboligena-settica localizzate in sede corticale temporo-frontale insulare sn (5 cm) e di minor dimensioni in sede fronto-temporo-parietale biemisferica, occipitale, talamica sinistra e cerebellare biemisferica; **alcune delle lesioni** descritte in sede occipitale e parietale posteriore biemisferica **presentano infarcimento ematico**.

Non si rilevano zone di rottura della BEE, né si rileva mismatch DWI/PWI.

Non idrocefalo.

Strutture della linea mediana in asse.

Le immagini angioRM dimostra **minor rappresentazione dei rami medio-distali della arteria cerebrale media sinistra**; non evidenziano stenosi né dilatazioni aneurismatiche a carico dei vasi del poligono di Willis e della arteria basilare.

Consulenza cardiochirurgica

“Ritengo vi sia indicazione chirurgica alla SVA anche se al momento le condizioni neurologiche suggeriscono una attesa di almeno 2 settimane. Da rivalutare in base alle condizioni cliniche.”

A **3 gg** dall'inizio della terapia specifica:

- CG migliorate
- Pz più reattivo, eloquio in miglioramento
- PA 120/70, FC 74R, sO2 97% in aa
- Apiretico

EMOCROMO/EMATICI	
Hb	11.3 g/dL
GB	**9 780 cell/mmc** ↓↓ (N 70%, L 17%)
PLT	343 000 cell/mmc
PCR	**5.74 mg/dL** ↓↓
Na+	137 mmol/L
K+	4 mmol/L

TOE
Valvola aortica tricuspide, con erosione della rima commissurale tra la cuspide non coronarica e la cuspide destra. Evidenza di **due piccole vegetazioni sulla cuspide sinistra e su quella non coronarica, di dimensioni inferiori a 0.5 cm**, ispessimento dell'anulus aortico dove è visualizzabile in corrispondenza della base di impianto tra cuspide non coronarica e sinistra immagine riferibile a **piccolo ascesso cavitato**, insufficienza aortica di grado severo.
Valvola mitrale con lembi fibrocalcifici ed evidenza di **piccole formazioni filiformi (inferiori a 0.2-0-3 cm)** adese al versante atriale del lembo mitralico anteriore e posteriore, insufficienza mitralica lieve.
Apparentemente indenne la giunzione mitroaortica, auricola monolobata con normali velocità flussimetriche di riempimento e svuotamento, non visualizzabili trombi al suo interno. Setto interatriale, in tutte le porzioni visualizzabili, apparentemente integro, non segni di shunt al color doppler.
Aorta toracica esente da placche ateromasiche.
Si consiglia rivalutazione cardiochirurgica.

Consulenza cardiochirurgica
Persiste indicazione alla cardiochirurgia, non con carattere di urgenza, compatibilmente con il quadro neurologico

Caso clinico:

B.C. donna, 74 anni

Anamnesi patologica remota:

- Ipertensione arteriosa, in trattamento farmacologico
- Dislipidemia
- Pregresso ricovero circa 25 anni fa per otite destra, complicata da mastoidite

Anamnesi patologica prossima:

Lombalgia con irradiazione all'arto inferiore destro e febbricola da Agosto 2022 per cui ha esegue accesso in PS esterno, dimessa con terapia sintomatica intramuscolare

Dopo due settimane nuovo accesso in PS per persistenza di febbre e comparsa di dispnea

In pronto soccorso

Esami ematici:

- leucocitosi neutrofila (GB 17300 cell/mmc, N 85.5%)
- PCR 22 mg/dl
- creatinina 1.48 mg/dl
- due set emocolture di cui una positiva per S. aureus MRSA

BATTERIOLOGIA

EMOCOL AEROB DA VENA PERIF. POSITIVA

Germe Identificato:

Microorganismo # 1 Staphylococcus aureus (STAAUR)

Tempo di positivizzazione (HH:MM) 10:30

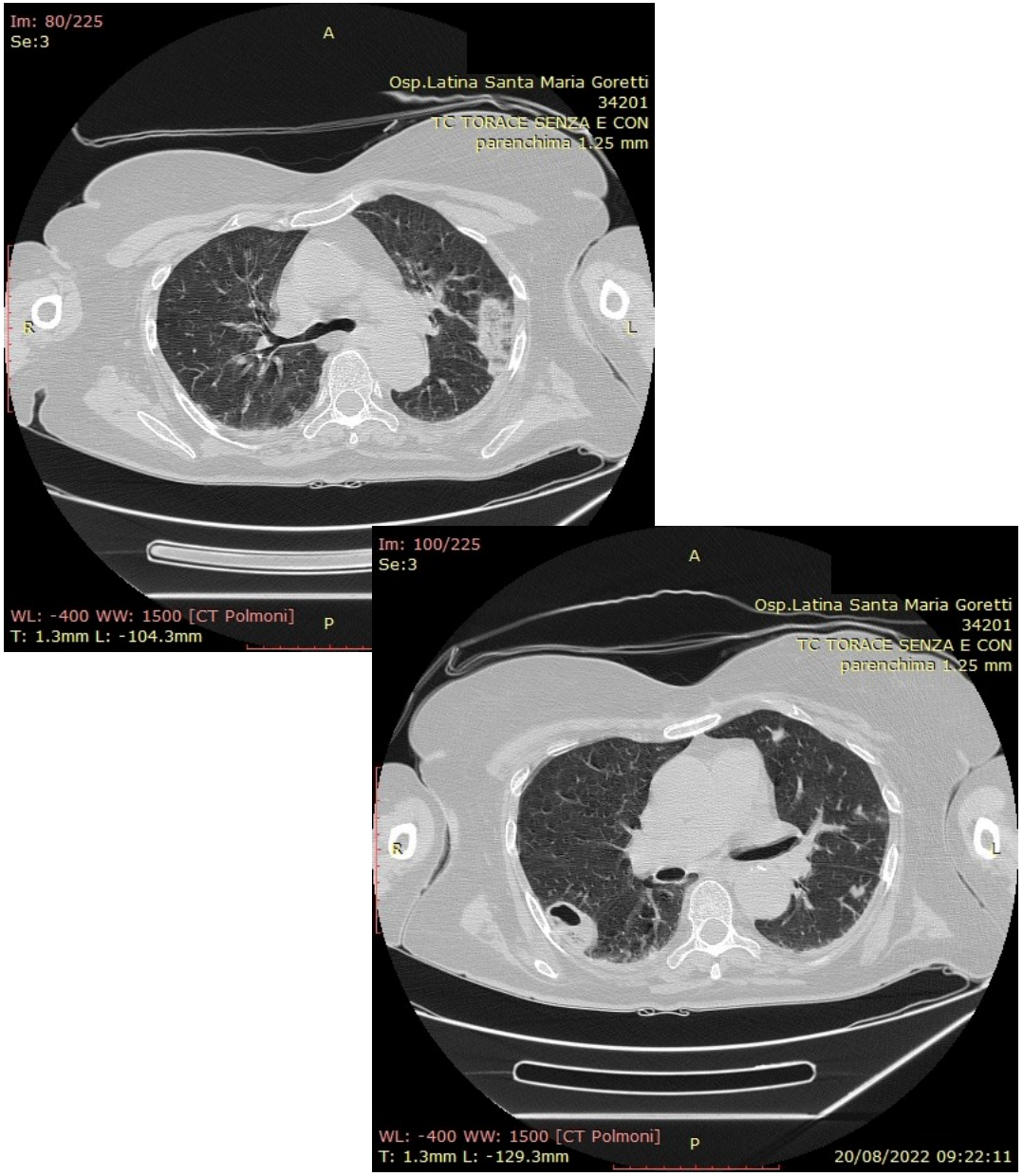
IE= Insufficiente Evidenza
Non esistono BreakPoint di interpretazione EUCAST per l'antibiotico
I= Sensibile se trattato ad alte dosi
(-)= Test di sensibilità non raccomandato

	1 STAAUR				
	SIR	MIC	SIR	MIC	SIR MIC
Acido Fusidico	S	<=0.5			
Cefoxitina screening	+	Pos			
Ceftarolina	S	0.25			
Clindamicina	S	0.25			
Eritromicina	S	0.5			
Gentamicina	R	8			
Levofloxacina	R	4			
Linezolid	S	2			
Mupirocine	S	<=1			
Oxacillina MIC	R	0.5			
Penicillina G	R	>=0.5			
R inducibile a Clindamicina	-	Neg			
Rifampicina	S	<=0.03			
Teicoplanina	S	<=0.5			
Tetraciclina	S	<=1			
Tigeciclina	S	<=0.12			
Trimetoprim/Sulfam.	S	<=10			
Vancomicina	S	1			

EMOCOLTURA ANAEROBI VENA PERIF NEGATIVO

TC torace (20/08):

addensamenti multipli sparsi su tutto l'ambito, a localizzazione mantellare e submantellare, i maggiori a livello del LSD e del LSS, con evidenti fenomeni escavativi. Altra lesione con stesse caratteristiche a livello del muscolo sottoscapolare sx

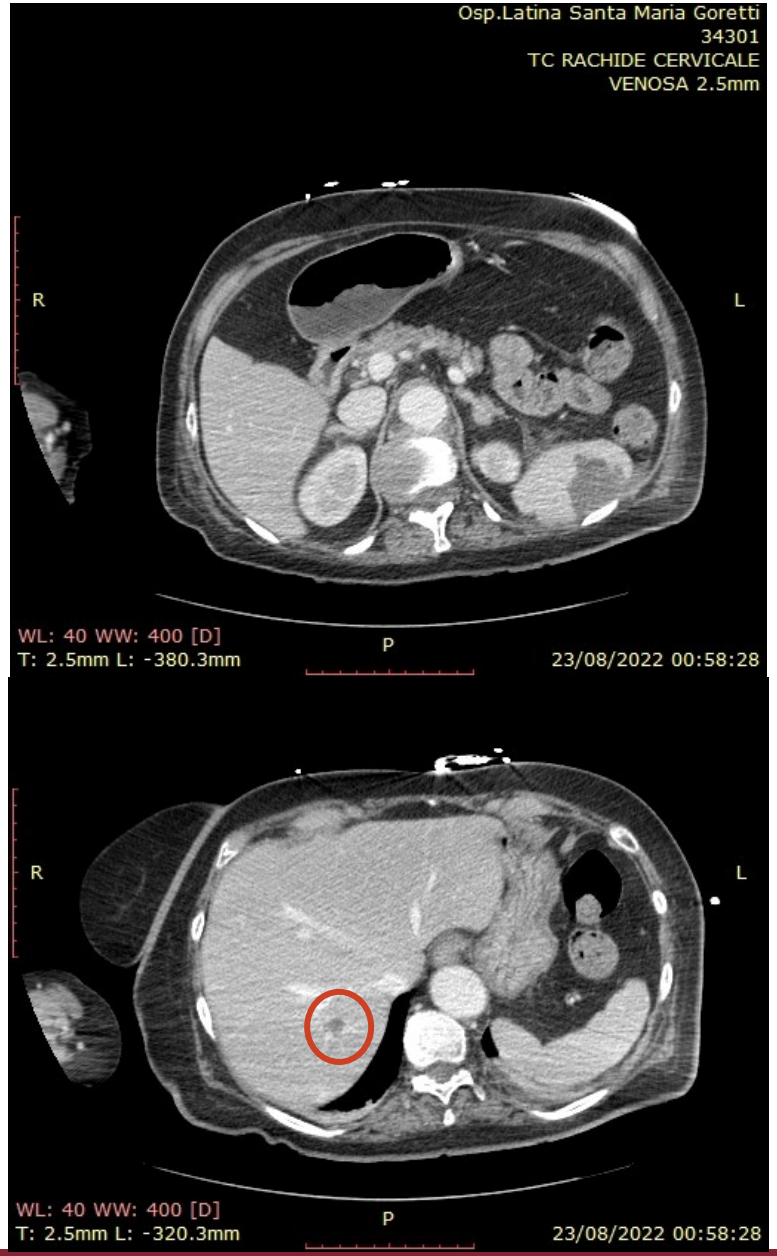


TC addome (23/08):

<u>Milza</u>: in corrispondenza del polo inferiore e laterale si segnala area ipodensa in tutte le fasi di acquisizione riferibile a zona di ipoperfusione-ischemica. Concomita minima falda fluida in sede perisplenica.

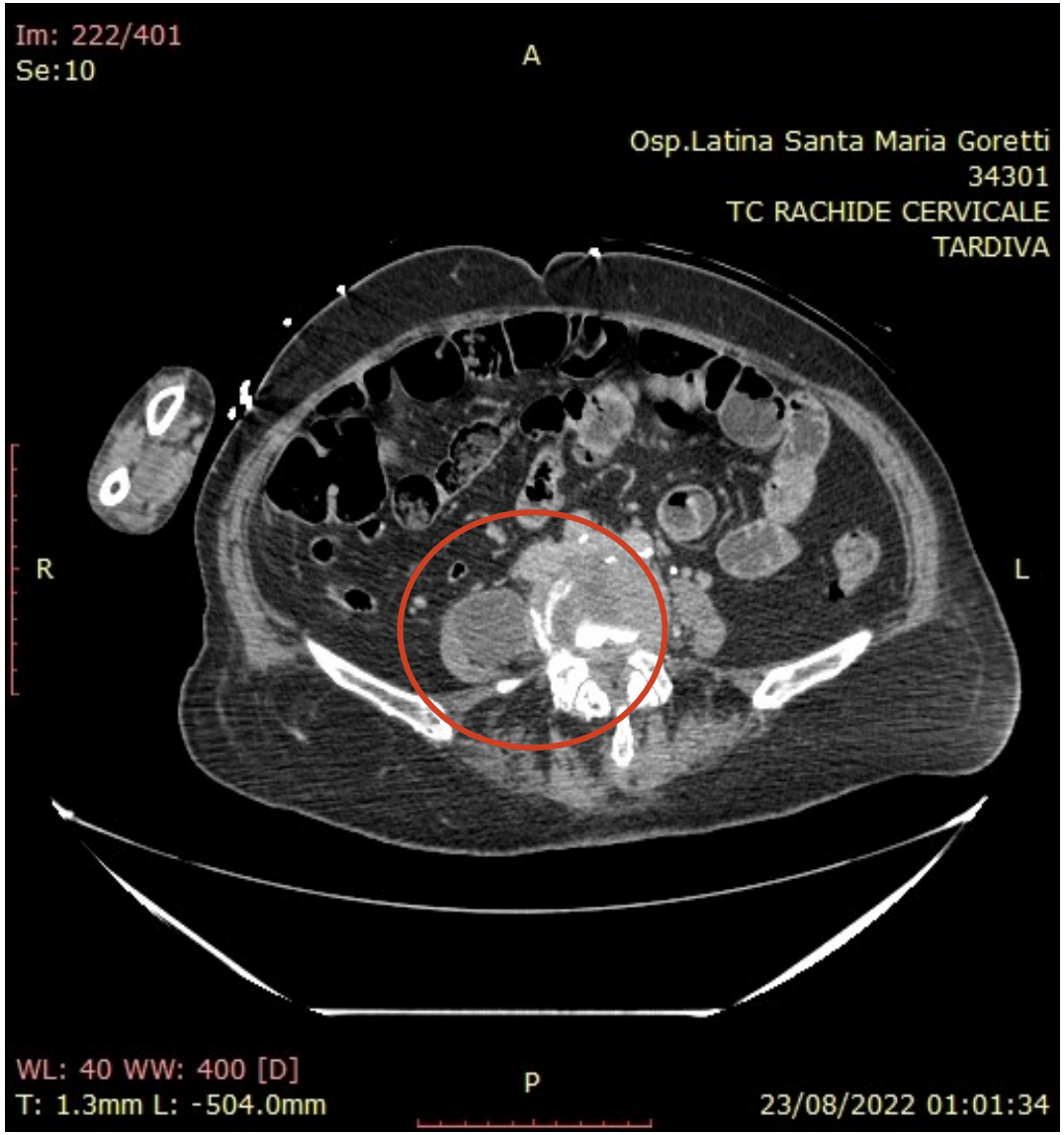
<u>Fegato</u>: dimensioni aumentate con profili regolari. A livello della VII - VI segmento si osservano alcune aree ipodense ravvicinate a morfologia allungata localizzate nelle regioni adiacenti ai rami portali, reperti di non univoca interpretazione

<u>Aorta addominale</u> diffusamente ateromasica. In corrispondenza della tratto di passaggio toraco-addominale si osserva ispessimento del tessuto adiposo localizzato tra aorta ed il versante anteriore dello spazio intersomatico di D12 - L1.



TC rachide (23/08):

aumento volumetrico del muscolo psoas di destra nel cui contesto si osserva formazione a contenuto fluido delle dimensioni massime di circa 40 x 30 mm (DAP xDT) per un'estensione longitudinale di circa 12 cm, da riferire in prima ipotesi a raccolta fluida intramuscolare. A livello della radice della coscia si segnala inoltre aspetto disomogeneamente ipodenso anche del muscolo retto del quadricipite sinistro.



Ricovero presso altro Nosocomio

Impostata terapia antibiotica con vancomicina+ piperacillina/tazobactam

Ecocardiogramma transtoracico (01/09): assenza di vegetazioni endocarditiche in atto

TC addome con mdc (07/09): disco intersomatico di L4-L5 a densità disomogenea, con area apparentemente fluido-ipodensa nel contesto. Reperto compatibile con spondilodiscite. Aneurisma dell'aorta addominale superiore al passaggio con l'aorta toracica (DM 52×39mm) non clivabile dal rachide a livello D12-L1.

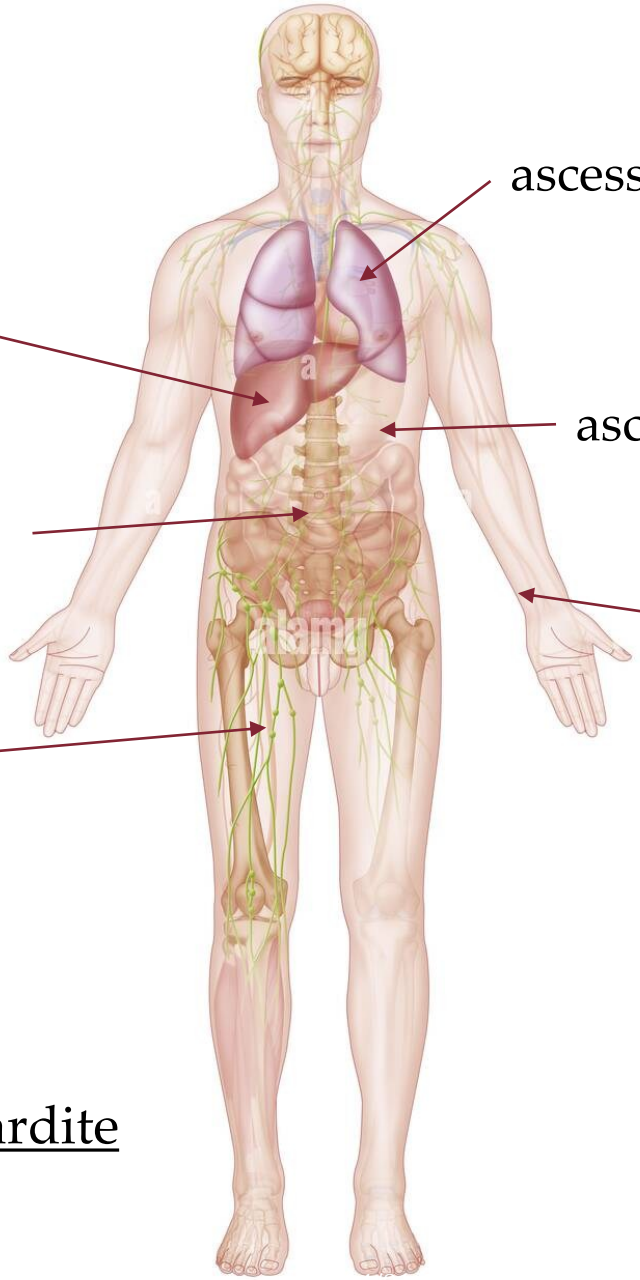
La paziente è stata quindi trasferita da noi

All’esame obiettivo

Condizioni cliniche generali mediocri, vigile, collaborante, orientata nel tempo e nello spazio, apiretica, eupnoica in aria ambiente, lamenta forte lombalgia

All'esame obiettivo del torace, MV lievemente ridotto su tutto l'ambito, crepitazioni bilaterali maggiormente presenti alla base di destra
Soffio olosistolico 3/6

All'ingresso



ascessi polmonari

ascessi epatici

ascessi splenici

Spondilodiscite L4-L5

emocoltura positiva S.aureus

ascessi muscolari

Cosa sospettare? → endocardite

Durante la degenza (1)

Ecocardiogramma transtoracico (08/09): valvola mitrale grossolanamente ispessita e con interessamento delle corde tendinee con immagine di plus riferibile in prima ipotesi a formazione endocarditica. Insufficienza valvolare severa

Emocolture di controllo 3 set (08/09): negative

Ecocardiogramma transesofageo (13/09): valvola mitrale con prolasso di entrambi i lembi, ispessiti con malcaptazione, insufficienza di grado medio-severo; valvola tricuspide con immagine di plus 0.5×0.4 cm sulla superficie atriale del lembo posteriore compatibile con massa vegetante. Insufficienza di grado moderato.

Durante la degenza (2)

Modificata terapia antibiotica: sospeso tazocin, proseguitaVancomicina 30 mg/kg/die

videat cardiochirurgico (13/09): non indicazioni chirurgiche

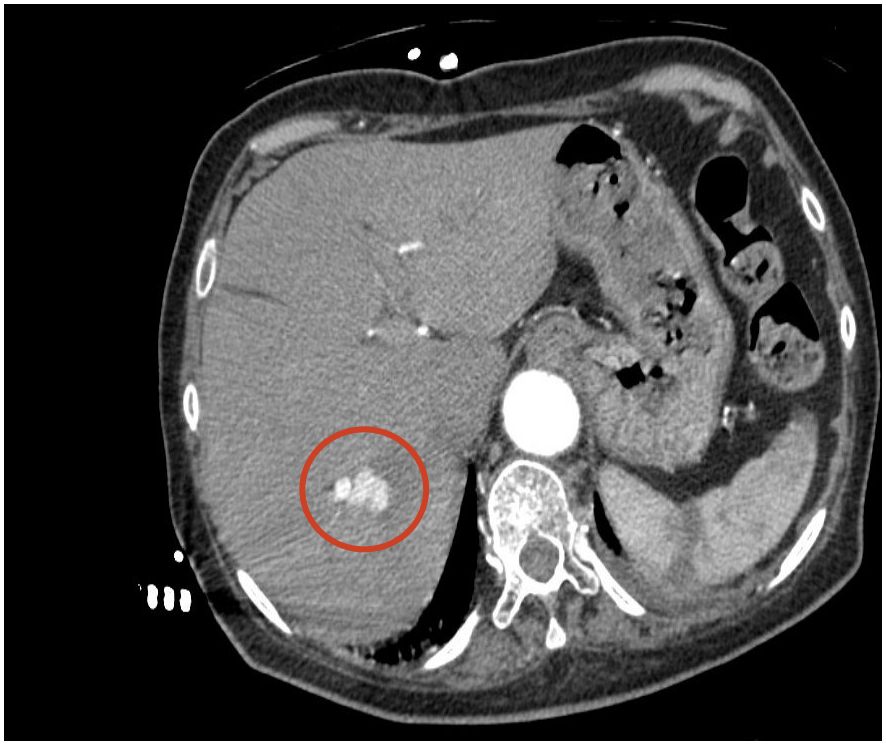
videat neurochirurgico (14/09): indicazione a posizionamento di busto

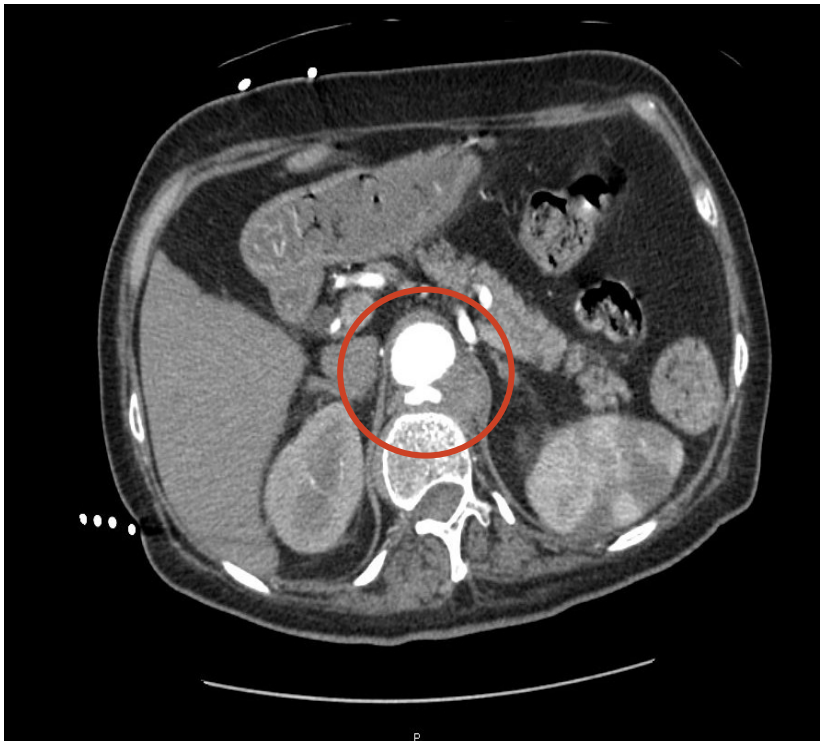
videat oculistico (14/09): fundus oculi nella norma

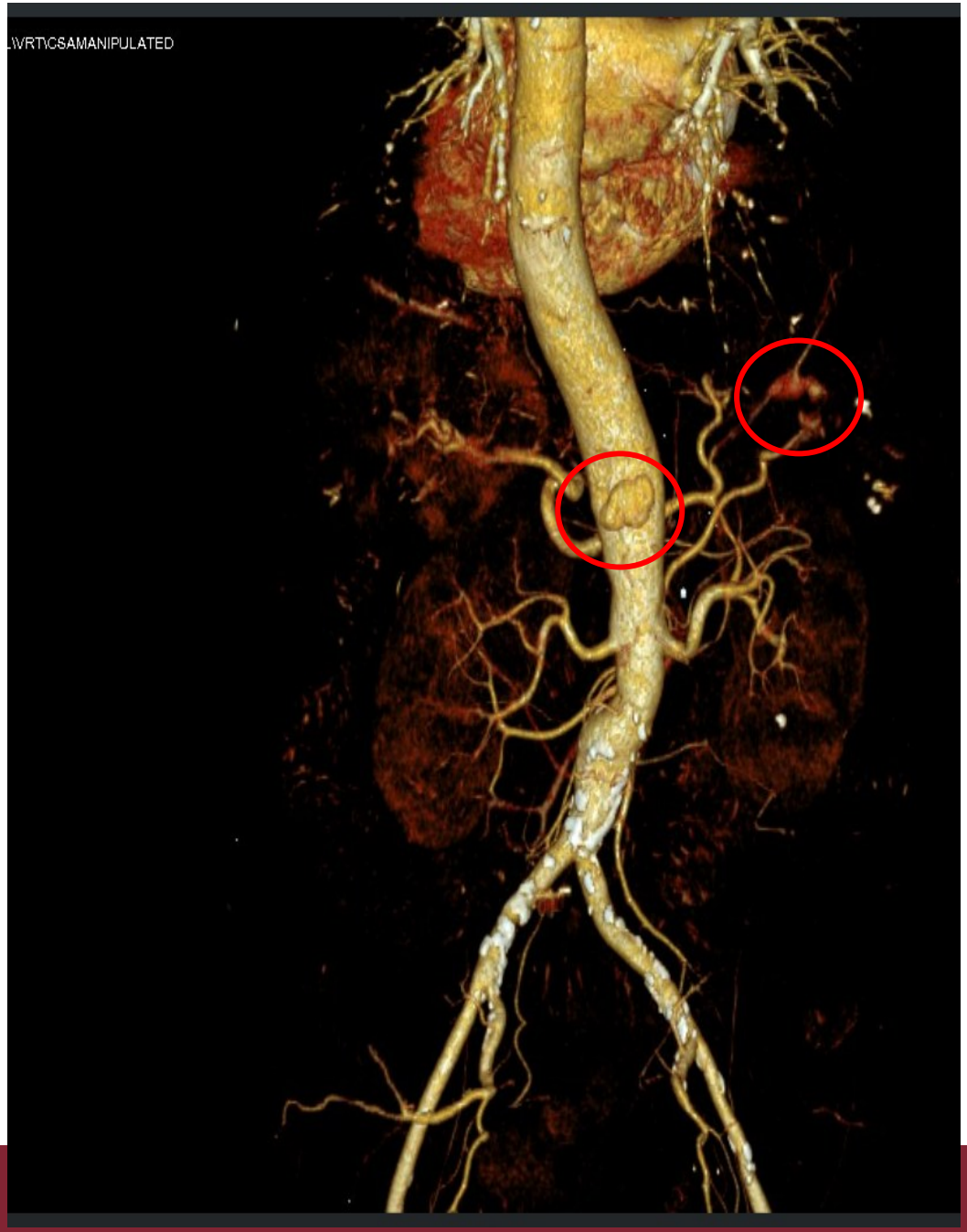
Per persistenza della lombalgia viene ripetuta TC addome e torace con mdc (14/09)

TC addome e torace con mdc (14/09):

presenza di pseudoaneurisma dell'aorta al passaggio toraco-addominale con aspetto di ulcera penetrante nel contesto del trombo eccentrico postero-laterale sx […] presente ulteriore pseudoaneurisma arterioso intraepatico nel contesto del VII segmento di circa 3.6 cm .






\VRT\CSAMANIPULATED

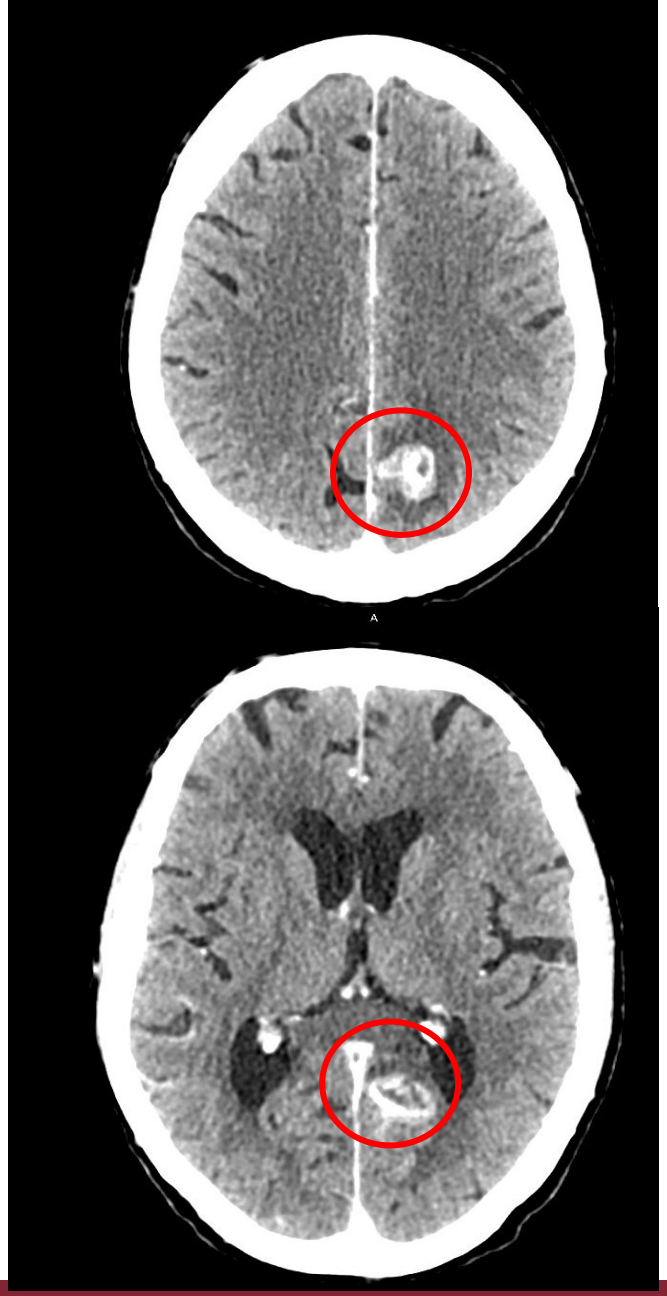
Durante la degenza (3)

Sottoposta ad intervento ch. vascolare (14/09) di embolizzazione con coil metallico dell'arteria epatica di destra per pseudoaneurisma con segni di sanguinamento attivo e posizionamento di endoprotesi aortica a livello del tripode celiaco per esclusione di pseudoaneurisma aortico.

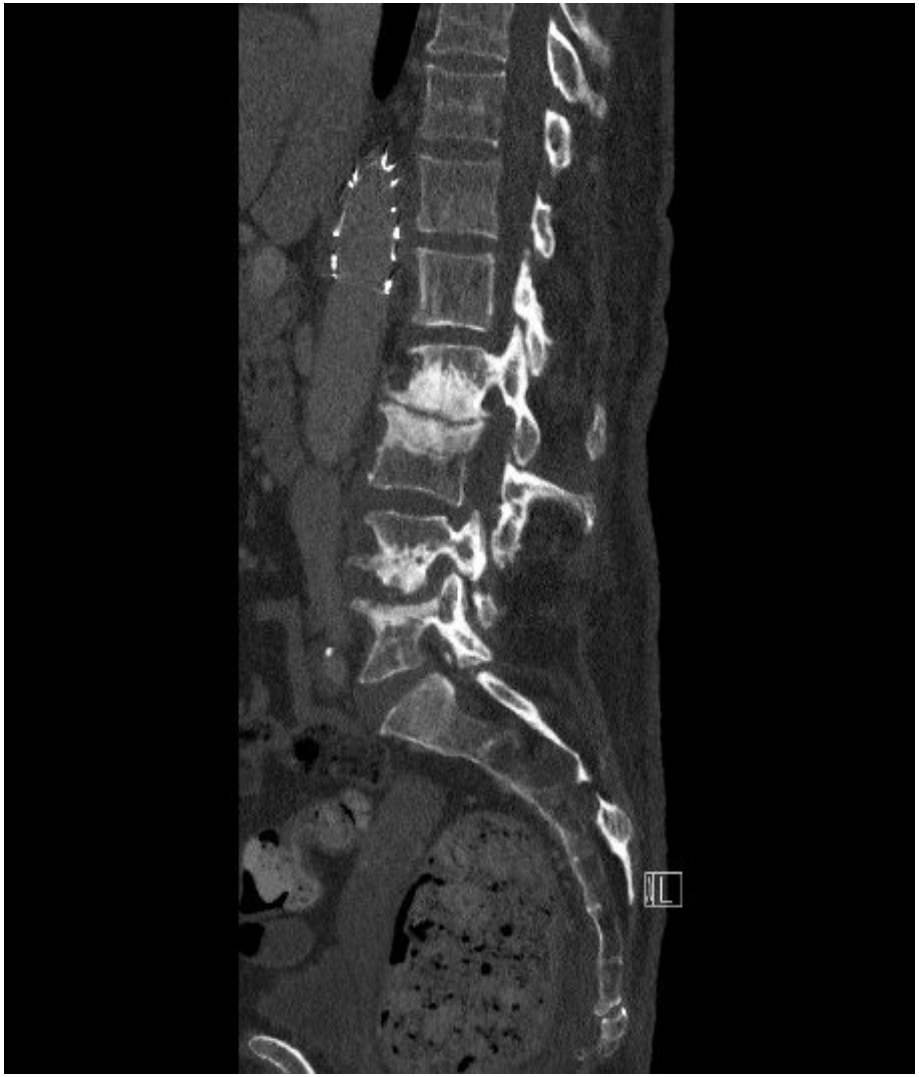
TC total body di controllo:

<u>Encefalo</u>: disomogenea area pluriloculata, con morfologia ramificata, estesa per complessivi 38mm circa, provvista di intenso potenziamento contrastografico come per ulteriori localizzazioni ascessuali in sede parenchimale cerebrale in sede parietale posteriore sinistra, con ramificazioni che raggiungono la falce ed ipodensità edematosa di aspetto digitato del parenchima circostante

Modificata terapia antibiotica in daptomicina 700 mg/die + ceftarolina 600 mg x3/die proseguita fino alla dimissione



<u>Addome e torace</u>: regolare opacizzazione del lume endoprotesico con esclusione della sacca ulcerata nel contesto del trombo eccentrico. Non opacizzato lo pseudoaneurisma arterioso intraepatico del VII°segmento dopo embolizzazione. Sostanzialmente invariati i restanti reperti toraco- addominali.



Ecocardiogramma transtoracico di controllo (14/10)

«funzione sistolica globale nella norma senza alterazioni cinetiche distrettuali. Valvola mitrale grossolanamente ispessita e con interessamento delle corde tendinee ed insufficienza valvolare severa [...] Persistente masserella verosimilmente adesa sul lembo settale della tricuspide, come evidenziato dall'ETE»

Dimessa in condizioni in condizioni cliniche generali discrete, apiretica ed eupnoica in aria ambiente. Agli ultimi esami ematici GB 3710 cell/mmc, PCR 0.86 mg/dl

Prosegue doxiciclina 100 mg x 2/die

Follow-up

Tomoscintigrafia globale corporea (24/10)

Torace: *lieve riduzione degli addensamenti polmonari; non presente uptake a livello endocardico*

Addome: *persiste aumentato uptake a livello del m. ileo-psoas di destra, che appare connesso ai somi L4-L5; aree di alterato uptake a livello splenico; ridotto l'uptake a livello dei mm. retto femorale e tensore della fascia lata di sinistra*

Encefalo: *area ipoattiva in sede parietale posteriore sinistra*

Seguita in regime DH ha in programma TC-TB, nuovo ecocardiogramma TT e prosegue doxiciclina

Staphylococcus aureus bacteremia (SAB)

- S*taphylococcus aureus* bacteremia (SAB) is common and frequently associated with poor outcomes.
- The estimated annual incidence of SAB is 5 to 40 cases per 100000 population and has been increasing inrecent decades because of increasing exposure to health care.
- Largely observational evidence indicates that specific care processes are associated with improved outcomes for patients with SAB, including early source control, use of echocardiography to identify endocarditis,appropriate antibiotic prescribing,and consultation with infectious diseases (ID) specialists to guide management

JAMA Internal Medicine | Original Investigation

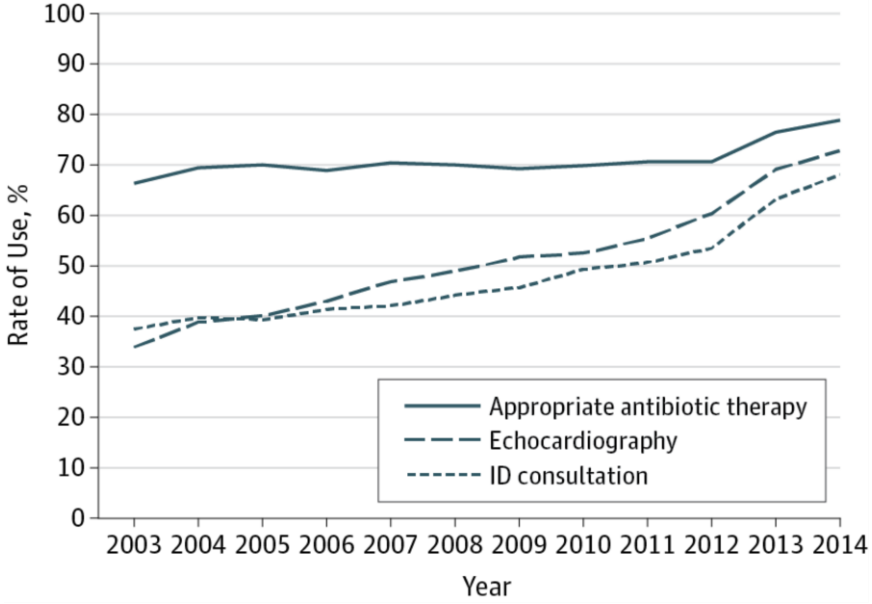
Association of Evidence-Based Care Processes With Mortality in *Staphylococcus aureus* Bacteremia at Veterans Health Administration Hospitals, 2003-2014

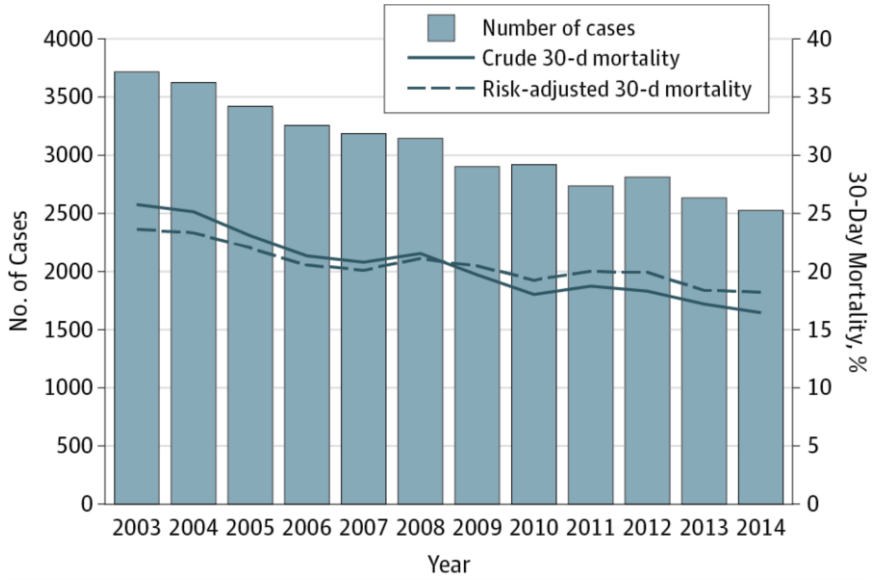
Michihiko Goto, MD, MSCI; Marin L. Schweizer, PhD; Mary S. Vaughan-Sarrazin, PhD; Eli N. Perencevich, MD, MS; Daniel J. Livorsi, MD, MS; Daniel J. Diekema, MD, MS; Kelly K. Richardson, PhD; Brice F. Beck, MA; Bruce Alexander, PharmD; Michael E. Ohl, MD, MSPH

JAMA Intern Med. 2017;177(10):1489-1497. doi:10.1001/jamainternmed.2017.3958
Published online September 5, 2017. Corrected on October 2, 2017.

From: **Association of Evidence-Based Care Processes With Mortality in Staphylococcus aureus Bacteremia at Veterans Health Administration Hospitals, 2003-2014**

JAMA Intern Med. 2017;177(10):1489-1497. doi:10.1001/jamainternmed.2017.3958



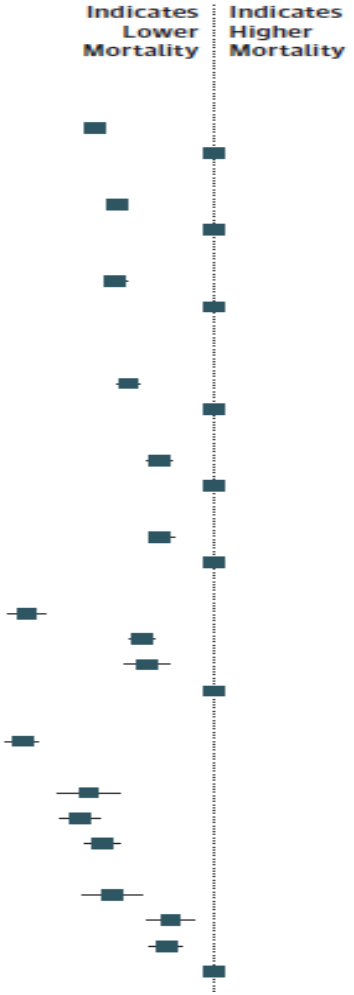


From: Association of Evidence-Based Care Processes With Mortality in Staphylococcus aureus Bacteremia at Veterans Health Administration Hospitals, 2003-2014

JAMA Intern Med. 2017;177(10):1489-1497. doi:10.1001/jamainternmed.2017.3958

Figure 3. Associations Between Receipt of Evidence-Based Care Processes and 30-Day Mortality

Evidence-Based Care Processes	No. of Patients (%)	Adjusted OR (95% CI)
Process measures (not adjusted for other care processes)		
ID consultation during hospitalization		
ID consultation	17 289 (46.9)	0.50 (0.47-0.53)
No ID consultation	19 579 (53.1)	1 [Reference]
Echocardiography during hospitalization		
Echocardiography	18 345 (49.8)	0.57 (0.53-0.60)
No echocardiography	18 523 (50.2)	1 [Reference]
Appropriate therapy during hospitalization		
Appropriate therapy	26 037 (70.6)	0.56 (0.52-0.60)
Other therapy	10 831 (29.4)	1 [Reference]
Process measures (adjusted for other care processes)		
ID consultation during hospitalization		
ID consultation	17 289 (46.9)	0.61 (0.56-0.65)
No ID consultation	19 579 (53.1)	1 [Reference]
Echocardiography during hospitalization		
Echocardiography	18 345 (49.8)	0.73 (0.68-0.78)
No echocardiography	18 523 (50.2)	1 [Reference]
Appropriate therapy during hospitalization		
Appropriate therapy	26 037 (70.6)	0.74 (0.68-0.79)
Other therapy	10 831 (29.4)	1 [Reference]
Types of echocardiography		
TEE	5522 (15.0)	0.33 (0.30-0.37)
TTE	10 769 (29.2)	0.66 (0.61-0.71)
Undocumented type	2054 (5.6)	0.67 (0.59-0.77)
No echocardiography	18 523 (50.2)	1 [Reference]
Combination of care processes		
All 3 care processes	10 608 (28.8)	0.33 (0.30-0.36)
Two of 3 care processes		
ID consultation and echocardiography	1382 (3.7)	0.48 (0.40-0.57)
ID consultation and appropriate therapy	4012 (10.9)	0.45 (0.40-0.51)
Echocardiography and appropriate therapy	4692 (12.7)	0.52 (0.47-0.58)
One of 3 care processes		
ID consultation only	1258 (3.4)	0.55 (0.46-0.66)
Echocardiography only	1663 (4.5)	0.78 (0.67-0.90)
Appropriate therapy only	6725 (18.2)	0.76 (0.69-0.83)
No care process	6528 (17.7)	1 [Reference]



Endocarditi infettive

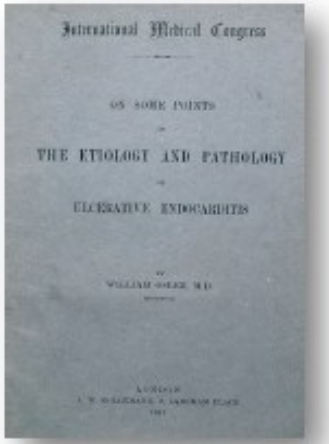
- **15.000-20.000 nuovi casi annuali**
- **4° principale causa di morte per sindrome infettiva (dopo sepsi urinaria, polmonite, e sepsi intra-addominale)**
- **Importanza di una diagnosi corretta, soprattutto ecocardiografica**
- **Precoce identificazione delle complicazioni**
- **Migliore strategie terapeutiche e di profilassi antimicrobica**

Evolution of knowledge from the early clinical description down to the early days of surgery…

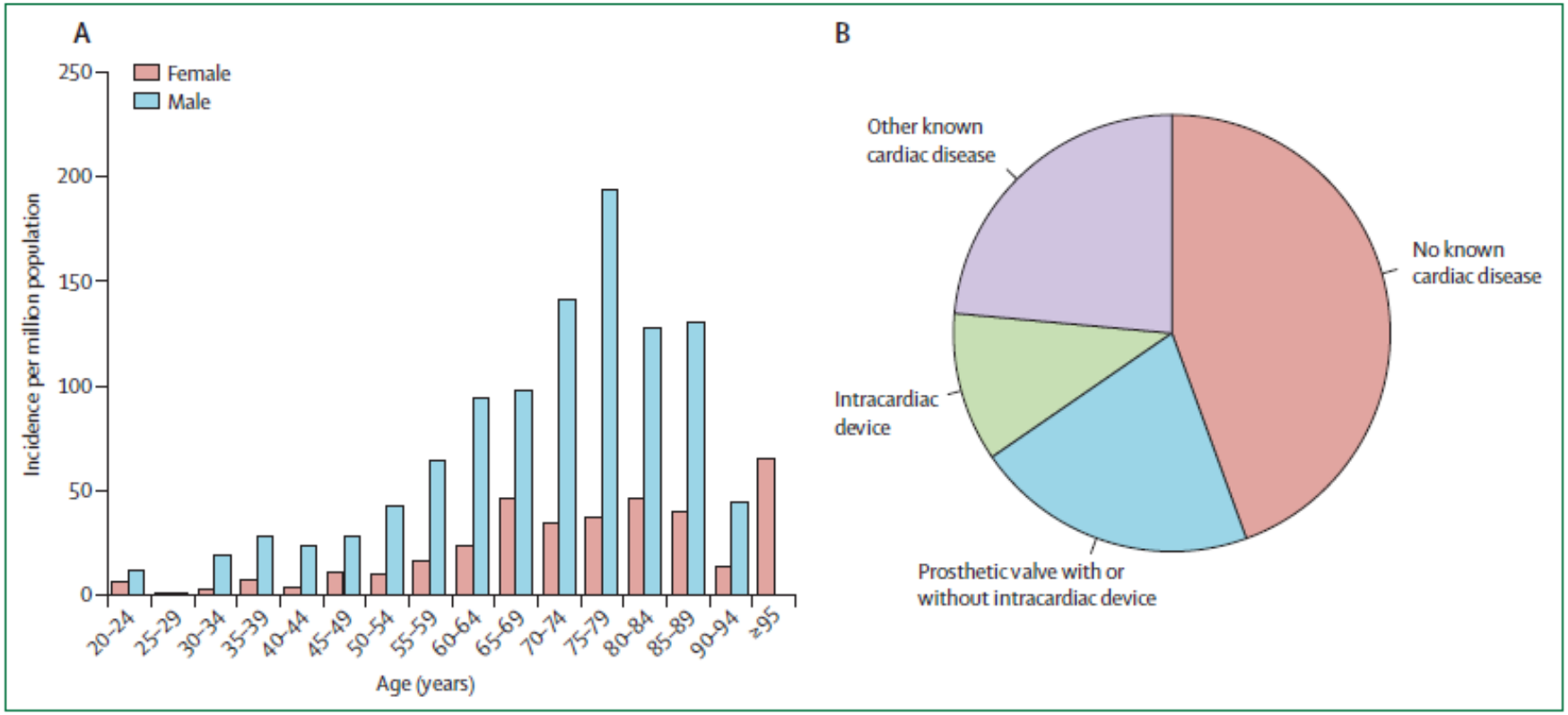
Jean Fernel
(1497-1558)

Lazare Riviere
(1589-1655)

William Osler
(1849-1919)



EPIDEMIOLOGY



Cahill TJ, Lancet 2016; 387: 882–93

Endocarditi infettive

Infezioni setticemiche a focolaio sepsigeno endocardico

- **Endocardite acuta**
  - **durata < 6 settimane**
  - **decorso tumultuoso**
  - **causata da germi altamente virulenti**
  - **frequente assenza di una pregressa cardiopatia**

- **Endocardite subacuta**
  - **durata > 6 settimane**
  - **decorso lento**
  - **causata da germi scarsamente virulenti**
  - **pregressa cardiopatia**

Epidemiologia

- **Incidenza annuale: 2-6/100.000**
- **Più frequente nel sesso maschile**
- **Età: > 60 anni nel 50% dei casi**
  - **riduzione della prevalenza della malattia reumatica**
  - **incremento malattie degenerative cardiache**
- **Emergenza di endocarditi nosocomiali**
- **Tossicodipendenza (< 40 anni)**

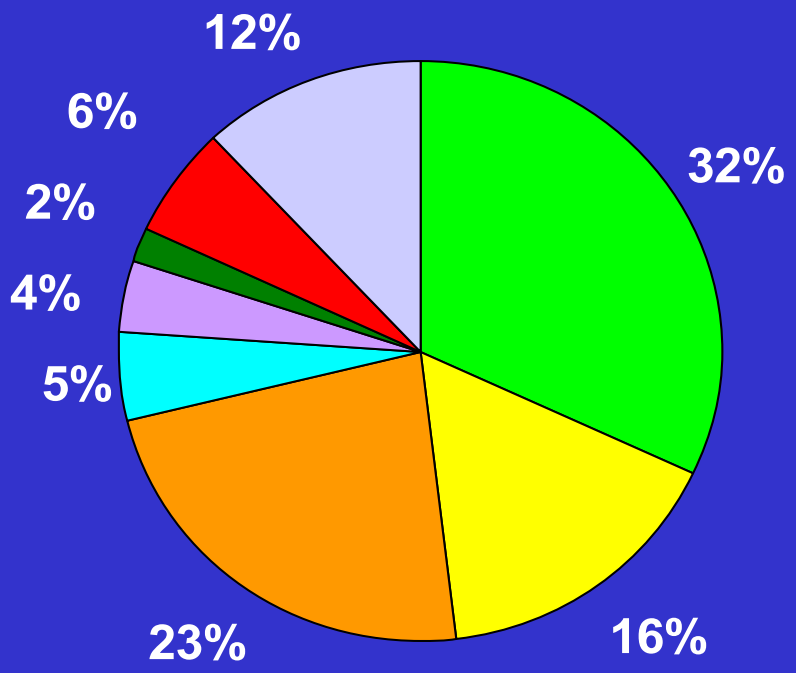
Endocarditi infettive (EI)

- **EI su valvola nativa (NVE)**
- **EI su valvola protesica (PVE): 7-25%**
- **EI in tossicodipendente (IVDA): 10-15%**
- **EI nosocomiale: 7-29%**

EZIOLOGIA (%)

Microrganismi	Valvola nativa	Valvola protesica
Streptococchi		
"viridanti"	60	10-30
S. pneumoniae	1-2	< 1
S. pyogenes	< 1	< 1
Enterococchi	10	5-10
Stafilococchi		
coagulasi neg.	< 1	25-30
S. aureus	25	15-20
Enterobatteri	< 5	< 5
Neisseria spp.	< 1	< 1
Candida spp.	< 1	5-10
Emocoltura neg.	< 5	< 5

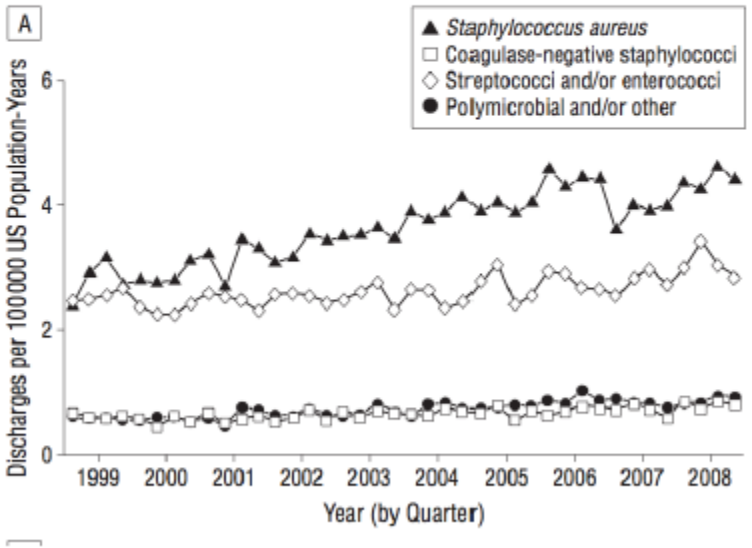
Eziologia



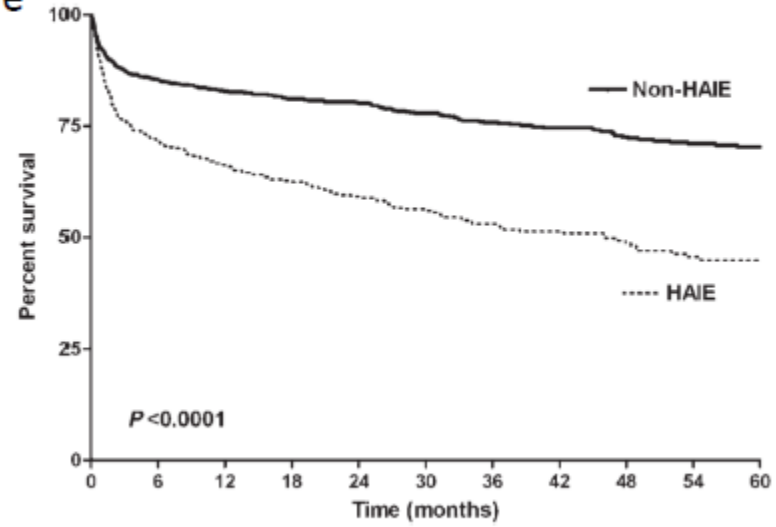
- *S. aureus*
- CONS
- viridans group
- *S. bovis*
- *E. faecalis*
- Gram neg
- "Emocoltura negativa"
- Altri

Increasing proportion of «Health care-associated IE»
30% of cases

Nosocomial
Long-term IV therapy
Hemodialysis
Home care



Federspiel JJ et al, et al. *Arch Intern Med* 2012;172:364-365

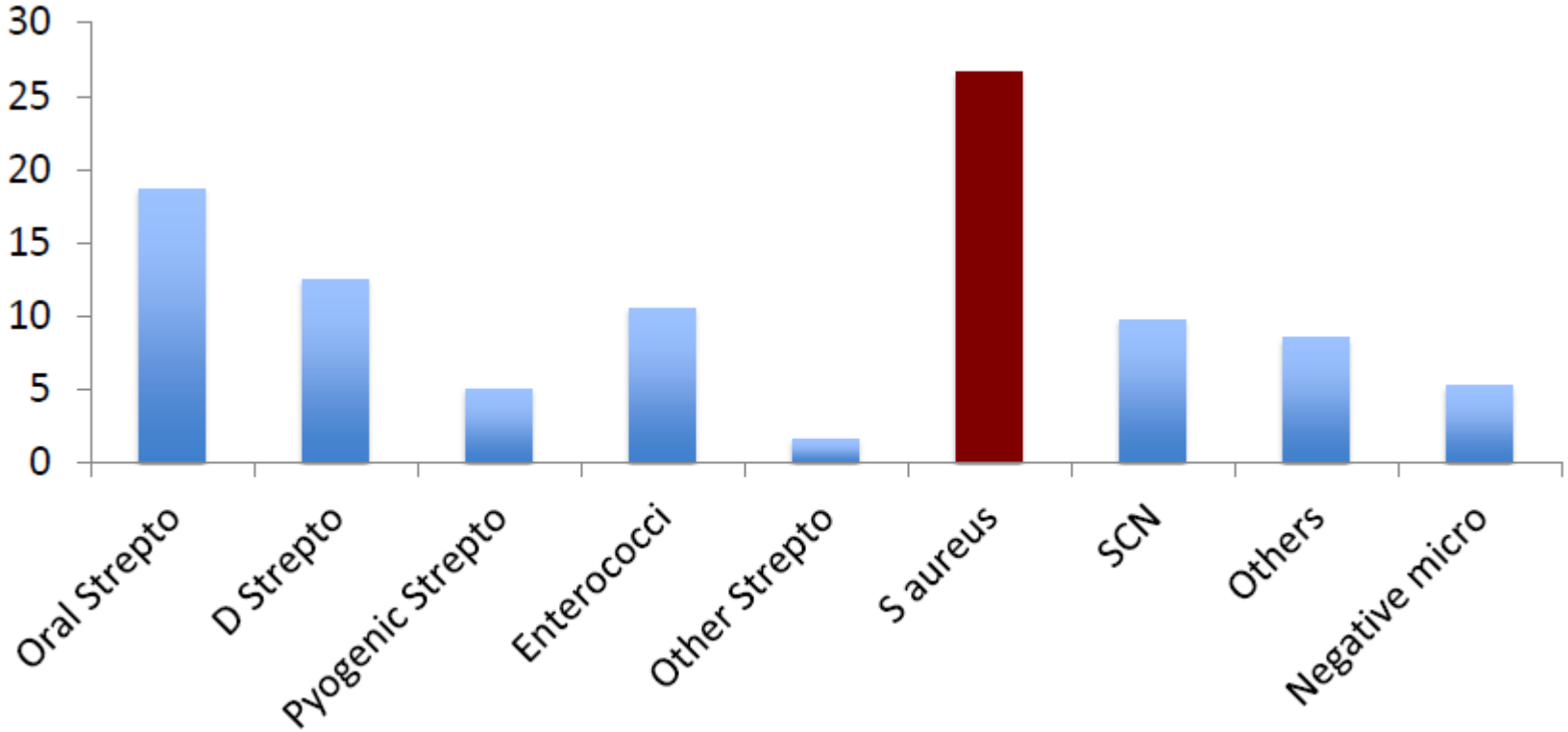


Sy RW, et al. *Eur Heart J* 2010;31:1890-1897

Epidemiological profile has changed

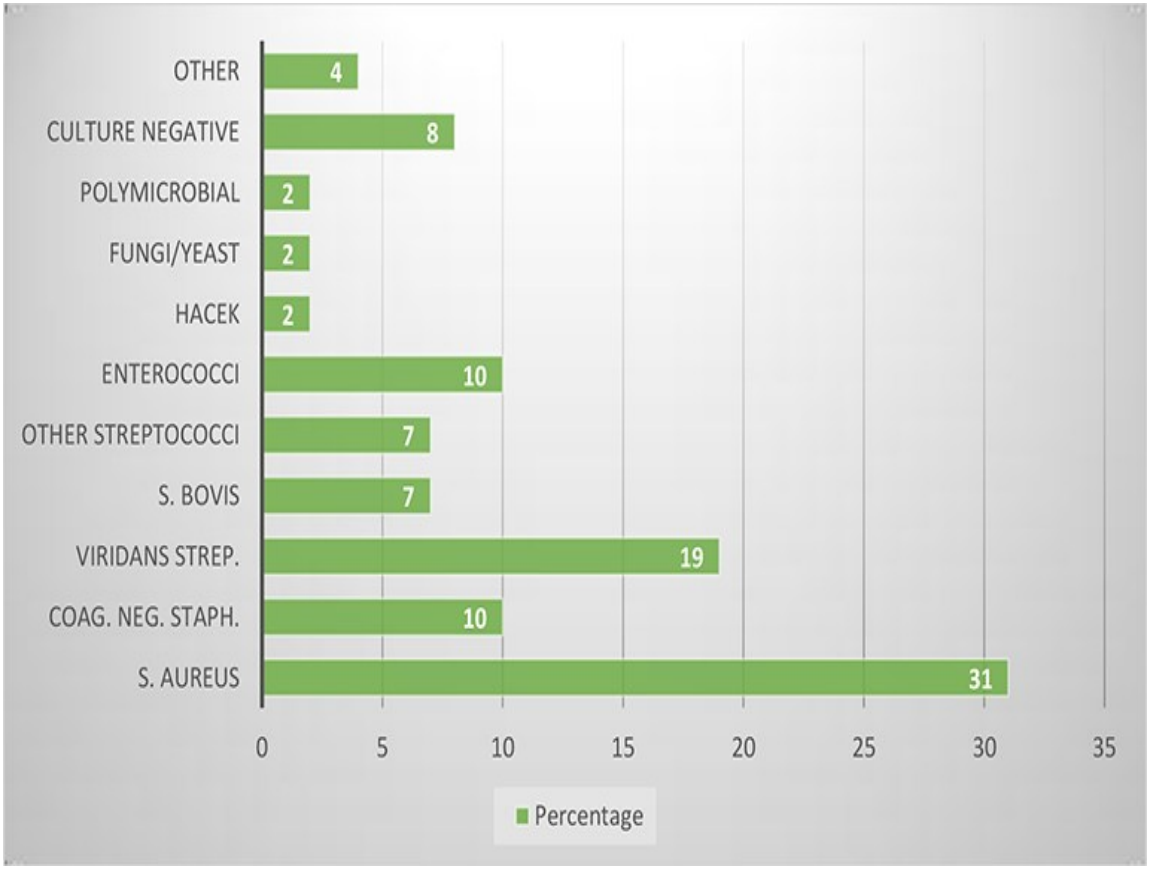
S aureus is the first causative pathogen

Circa il 30-60% delle batteriemie da *Staphylococcus aureus sono* complicate dall'insorgenza di un'endocardite infettiva.



Selton-Suty C, et al. Clin Infect Dis 2012;54:1230-9

Eziologia



Infective endocarditis in Italy

Table 2 Microbial etiology by site of acquisition

	Ca-IE, *n* (%)	NHCa-IE, *n* (%)
S. aureus	145/743 (19.5)	28/67 (41.8)
CoNS	67/743 (9.0)	7/67 (10.4)
Enterococcus spp.	92/743 (12.4)	6/67 (8.9)
S. bovis	94/743 (12.6)	2/67 (3.0)
Viridans streptococci	167/743 (22.5)	5/67 (7.5)
Other streptococci	31/743 (4.2)	–
Fungi	6/743 (0.8)	4/67 (6.0)
Others	38/743 (5.1)	2/67 (3.0)
Polymicrobial	26/743 (3.5)	5/67 (7.5)
Negative findings	77/743 (10.4)	8/67 (11.9)

Ca-IE community-associated IE,
NHCa-IE nosocomial health care-associated IE

Table 3 Microbial etiology of PV-IE by time of acquisition

	Early PV-IE, *n* (%)	Late PV-IE, *n* (%)
S. aureus	14/41 (34.1)	37/235 (15.7)
CoNS	10/41 (24.4)	39/235 (16.6)
Enterococcus spp.	5/41 (12.2)	44/235 (18.7)
S. bovis	2/41 (4.9)	25/235 (10.6)
Viridans streptococci	–	22/235 (9.4)
Other streptococci	–	6/235 (2.5)
Fungi	1/41 (2.4)	7/235 (3.0)
Others	5/41 (12.2)	18/235 (7.6)
Polymicrobial	2/41 (4.9)	10/235 (4.2)
Negative findings	2/41 (4.9)	27/235 (11.5)

The denominator denotes the actual number of cases for whom the data were recorded in the case report form

PV-IE prosthetic valve IE

Fabian Andres Giraldo. "Epidemiology of Infective Endocarditis." *Contemporary Challenges in Endocarditis*. InTech, 2016.

Cecchi, Enrico, et al. "Clinical epidemiology in Italian Registry of Infective Endocarditis (RIEI): Focus on age, intravascular devices and enterococci." *International journal of cardiology* 190 (2015): 151-156.

Taylor & Francis
Taylor & Francis Group

Expert Review of Anti-infective Therapy

ISSN: 1478-7210 (Print) 1744-8336 (Online) Journal homepage: http://www.tandfonline.com/loi/ierz20

Candida endocarditis: systematic literature review from 1997 to 2014 and analysis of 29 cases from the Italian Study of Endocarditis

Simone Giuliano, Maurizio Guastalegname, Alessandro Russo, Marco Falcone, Veronica Ravasio, Marco Rizzi, Matteo Bassetti, Pierluigi Viale, Maria Bruna Pasticci, Emanuele Durante-Mangoni & Mario Venditti

Endocarditi su valvola nativa
Microbiologia

Microrganismo	*Numero di casi (%)* *Comunitarie*	*Nosocomiali*
Streptococchi	220 (32)	6 (7)
Pneumococchi	8 (1)	
S. aureus	24 (35)	45 (55)
Stafilococchi coagulasi-negativi	29 (4)	8 (10)
Enterococco	57 (8)	13 (16)
Bacilli gram-negativi	25 (4)	4 (5)
HACEK	22 (3)	
Funghi	5 (1)	3 (4)
Polimicrobiche/Misc.	38 (6)	1 (1)
Emocoltura negativa	38 (6)	2 (2)
TOTALE	683	82

Endocarditi su valvola protesica
Microbiologia

Microrganismo	*NUMERO DI CASI (%)*		
	Tempo dall'intervento chirurgico		
	≤ 2 mesi N=161	*> 2-12 mesi N=31*	*> 12 mesi N=194*
Streptococchi	**5 (3)**	**3 (9)**	**61 (31)**
Pneumococchi	**----**	**----**	**----**
Enterococchi	**13 (8)**	**4 (12)**	**22 (11)**
Staphylococcus aureus	**36 (22)**	**4 (12)**	**34 (18)**
Stafilococchi coagulasi-negativi	**51 (32)**	**11 (32)**	**22 (11)**
Fastidious organisms (HACEK)	**----**	**----**	**11 (6)**
Bacilli gram-negativi	**19 (11)**	**1 (3)**	**11 (6)**
Funghi, Candida spp	**12 (7)**	**4 (12)**	**3 (1)**
Polimicrobiche/miscellanea	**4 (2)**	**2 (6)**	**9 (5)**
Difteroide	**9 (5)**	**---**	**5 (3)**
Emocoltura negativa	**7 (7)**	**2 (6)**	**16 (8)**

Endocarditi nel tossicodipendente
Microbiologia

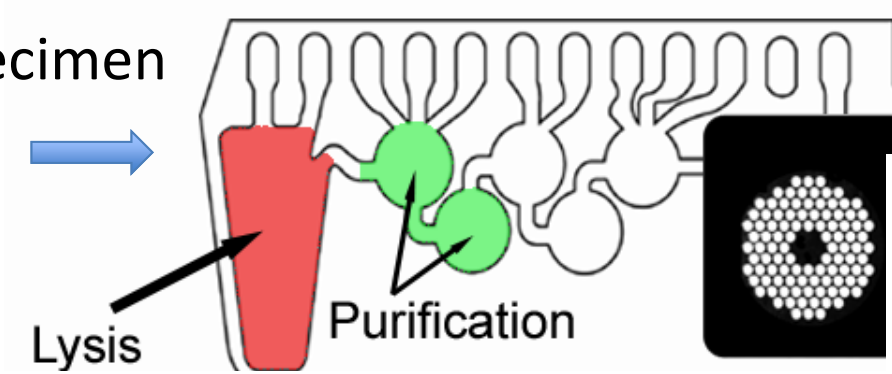
Microrganismo	Numero di casi (%)		
	Cuore Dx N = 346	Cuore Sn N = 204	Totale N = 550
S. aureus	265 (77)	48 (23)	313 (57)
Streptococchi	19 (5)	31 (15)	50 (9)
Enterococchi	6 (2)	49 (24)	55 (10)
Bacilli gram-negativi#	18 (5)	24 (12)	42 (7)
Fungi (predom. Candida sp.)	0 (0)	25 (12)	25 (5)
Polimicrobiche	21 (6)	14 (7)	35 (6)
Emocoltura negativa	9 (3)	7 (3)	16 (3)
Altri	8 (2)	6 (3)	14 (3)

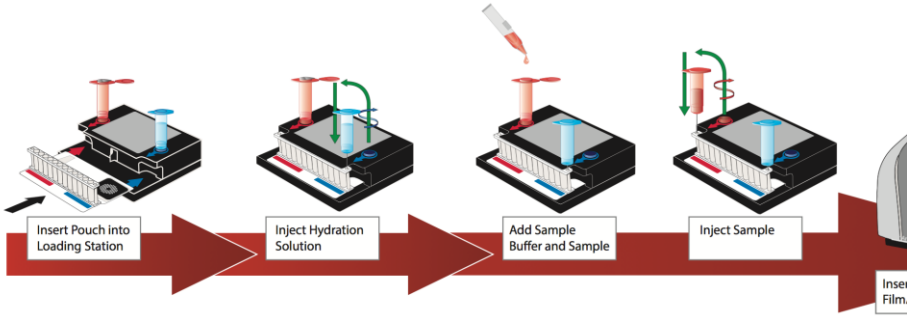
 # P. aeruginosa, *S. marcescens*, e Enterobacteriaceae

High multiplexed PCR

Microarray detection of:
- Species-specific genes
- Resistance genes

Specimen





Automation

TTR: 1h

"Syndromic" panels

Category	Target
Gram-negative bacteria	*Enterobacteriaceae*
	Escherichia coli
	Enterobacter cloacae complex
	Klebsiella oxytoca
	Klebsiella pneumoniae
	Serratia marcescens
	Proteus spp.
	Acinetobacter baumannii
	Haemophilus influenzae
	Neisseria meningitidis
	Pseudomonas aeruginosa
Gram-positive bacteria	*Staphylococcus* spp.
	Staphylococcus aureus
	Streptococcus spp.
	Streptococcus agalactiae
	Streptococcus pyogenes
	Streptococcus pneumoniae
	Enterococcus spp.
	Listeria monocytogenes
Fungi	*Candida albicans*
	Candida glabrata
	Candida krusei
	Candida parapsilosis
	Candida tropicalis
Antibiotic resistance markers	*mecA*
	vanA/vanB
	KPC

Endocarditi ad emocoltura negativa

- **Terapia antibiotica già iniziata**
- **Presenza di germi difficili: "fastidious organisms"**
  - **Listerie**
  - **Brucelle**
  - ***Corynebacterium Jeikeium***
  - **Legionelle**
  - ***Abiotrophia* species**
  - **Chlamydie**
  - **Bartonelle (*B. henselae, B. quintana, B. elizabethae*)**
  - **germi del gruppo HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*)**

Patogenesi

Pregressa lesione endocardica

Condizioni predisponenti

- Valvulopatie aterosclerotiche calcifiche: 40%
- Prolasso della valvola mitrale: rischio ↑5x-8x
- Cardiopatia reumatica: < 20%
- Cardiopatie congenite (persistenza dotto di Botallo, difetto del setto interventricolare, coartazione aortica, tetralogia di Fallot)
- Interventi di cardiochirurgia (protesi valvolari, cateterismo intravascolare)
- Elettrodi di pace-maker intracardiaci
- Tossicodipendenza per via ev

Storia naturale

- Penetrazione del germe causale attraverso le più diverse porte d'entrata (estrazioni dentali, tonsillectomia, cateterizzazioni, ecc.)
- Batteriemia
- Impianto dei batteri e formazione del focolaio sepsigeno sui lembi valvolari, corde tendinee o anche endocardio murale
- Sepsi alimentata dall'immissione in circolo di emboli batterici
- Formazione di infarti asettici o di focolai metastatici suppurativi
- Produzione di anticorpi e formazione di immunocomplessi circolanti (fenomeni vasculitici, cutanei, ecc.)

Anatomia patologica

- **Presenza di vegetazioni polipoidi (lembi valvolari, corde tendinee, endocardio murale, plastiche cardiache)**
- **Le vegetazioni sono costituite da ammassi di fibrina, piastrine, globuli rossi, globuli bianchi e microrganismi**
- **Colore: grigio-rossatro**
- **Numero e dimensioni: variabili**
- **Avascolari**
- **Estremamente friabili**

Anatomia patologica

- **Embolizzazioni multiple nel grande e piccolo circolo (cervello, reni, polmone)**
- **Aneurismi micotici: 10-15% dei casi**
- **Milza: iperplasia follicolare e proliferazione reticolare, infarti**
- **Reni: glomerulonefrite diffusa e glomerulonefrite a focolai (nefrite embolica parcellare di Lohlein)**

Quadro clinico

- Fenomeni infettivi generali
- Fenomeni cardiaci
- Fenomeni embolici (13-87%)
- Manifestazioni cutanee
- Fenomeni da immunocomplessi
  - glomerulonefrite diffusa e parcellare

Fenomeni infettivi generali

- **febbre**
- **astenia**
- **pallore**
- **calo ponderale**
- **mialgie e artralgie diffuse**
- **splenomegalia**

Fenomeni cardiaci

- **soffio persistente: 85% dei casi**
- **variazioni di intensità e timbro**
- **comparsa di nuovi soffi o rumori**
- **fibrillazione**
- **scompenso**
- **alterazioni ECG: non significative**

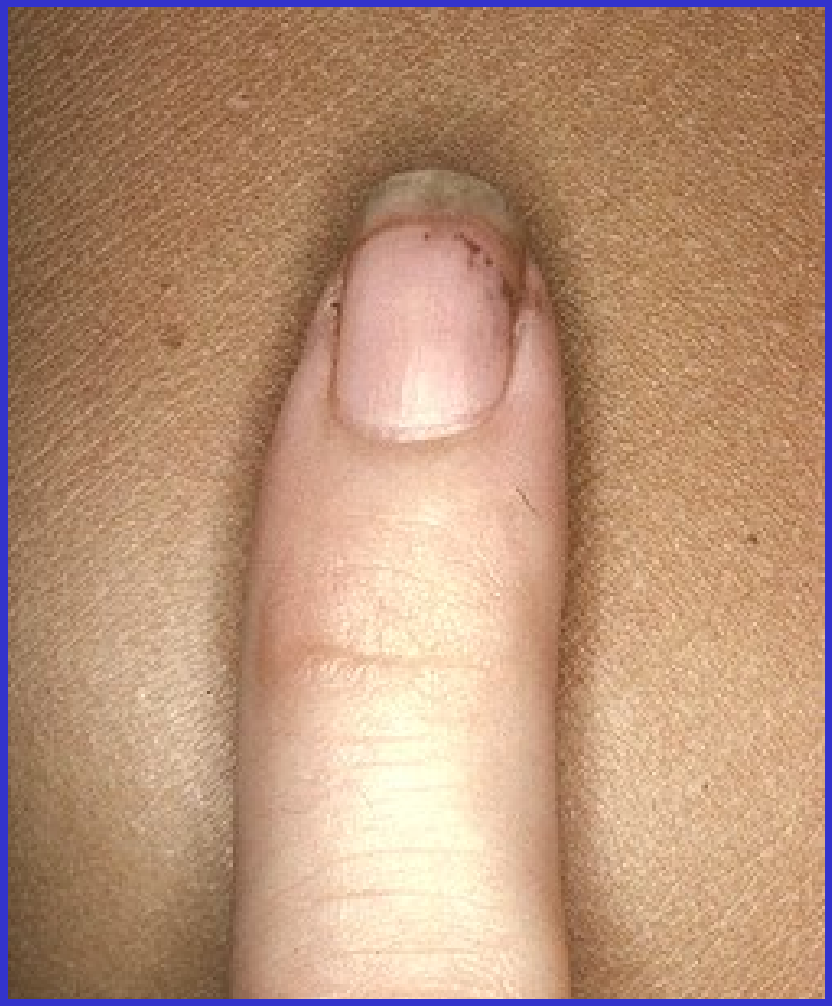
Fenomeni embolici

- **emboli settici e asettici**
- **milza: infarto splenico**
- **cervello: deficit motori e sensitivi, atassa, afasia**
- **coronarie: infarto del miocardio**
- **rene: nefrite embolica parcellare di Lohlein**
- **retina: amaurosi**
- **vasa vasorum: aneurismi**
- **endocardite destra: embolie polmonari**

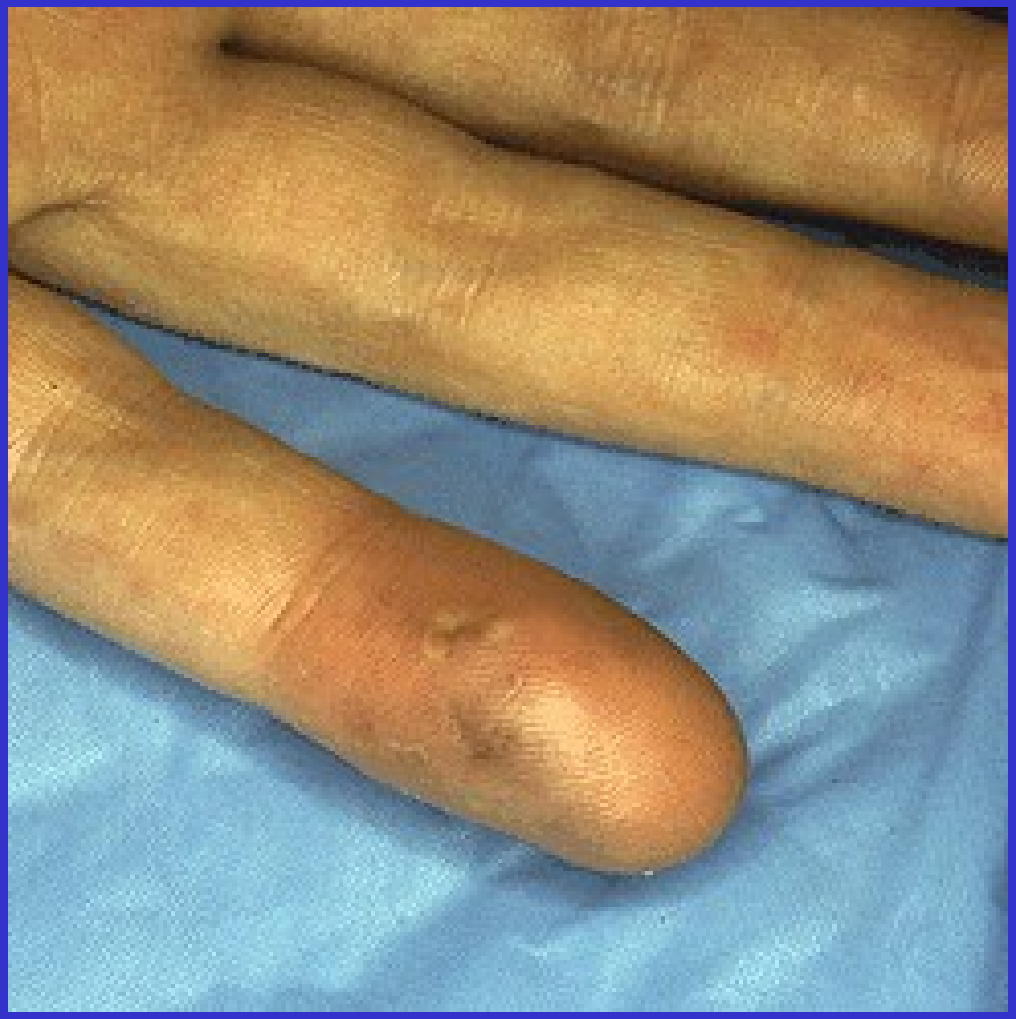
Fenomeni da immunocomplessi

- **glomerulonefrite diffusa o parcellare**
- **endoteliti e vasculiti**

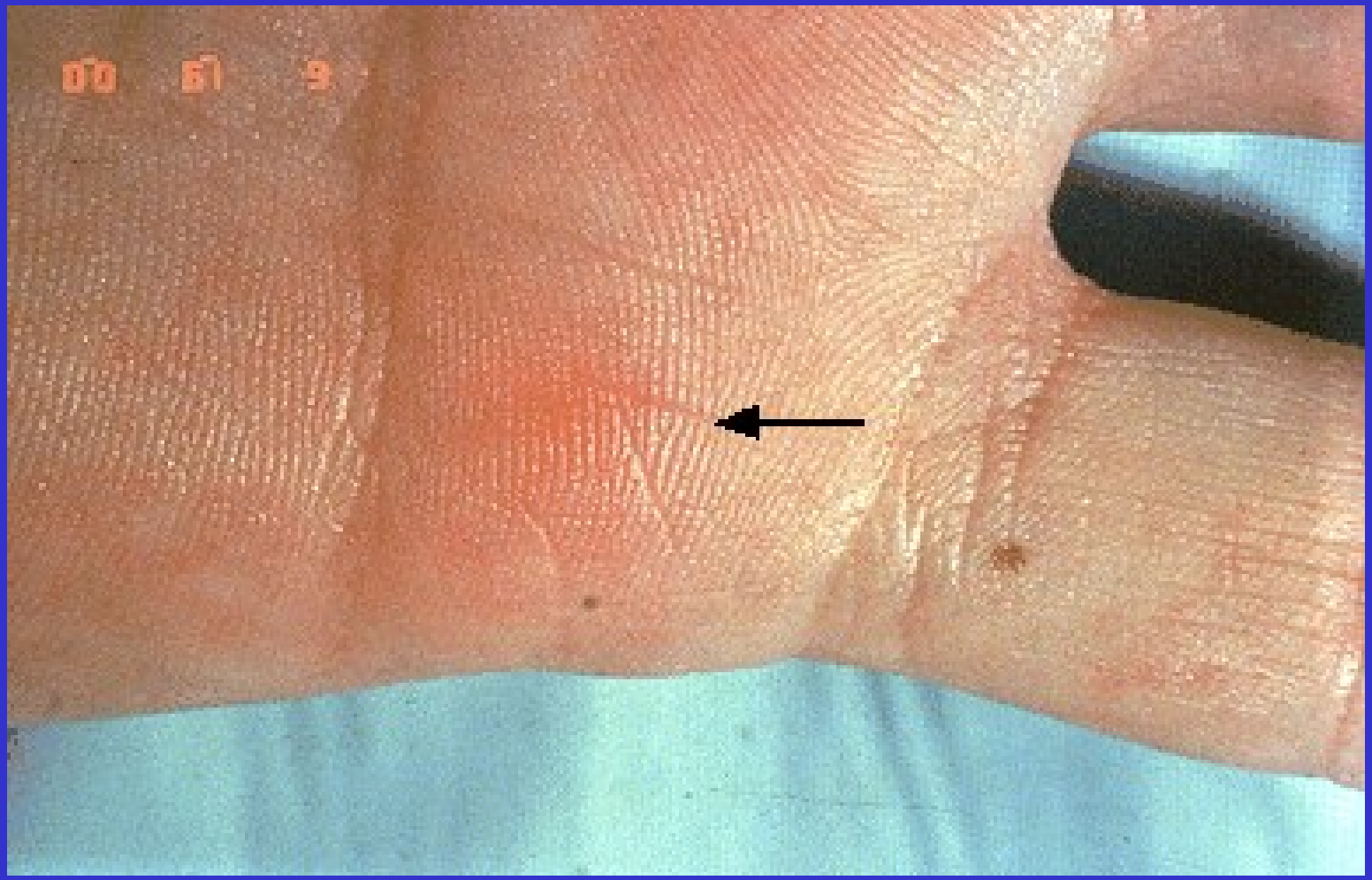
Emorragie a scheggia



Noduli di Osler

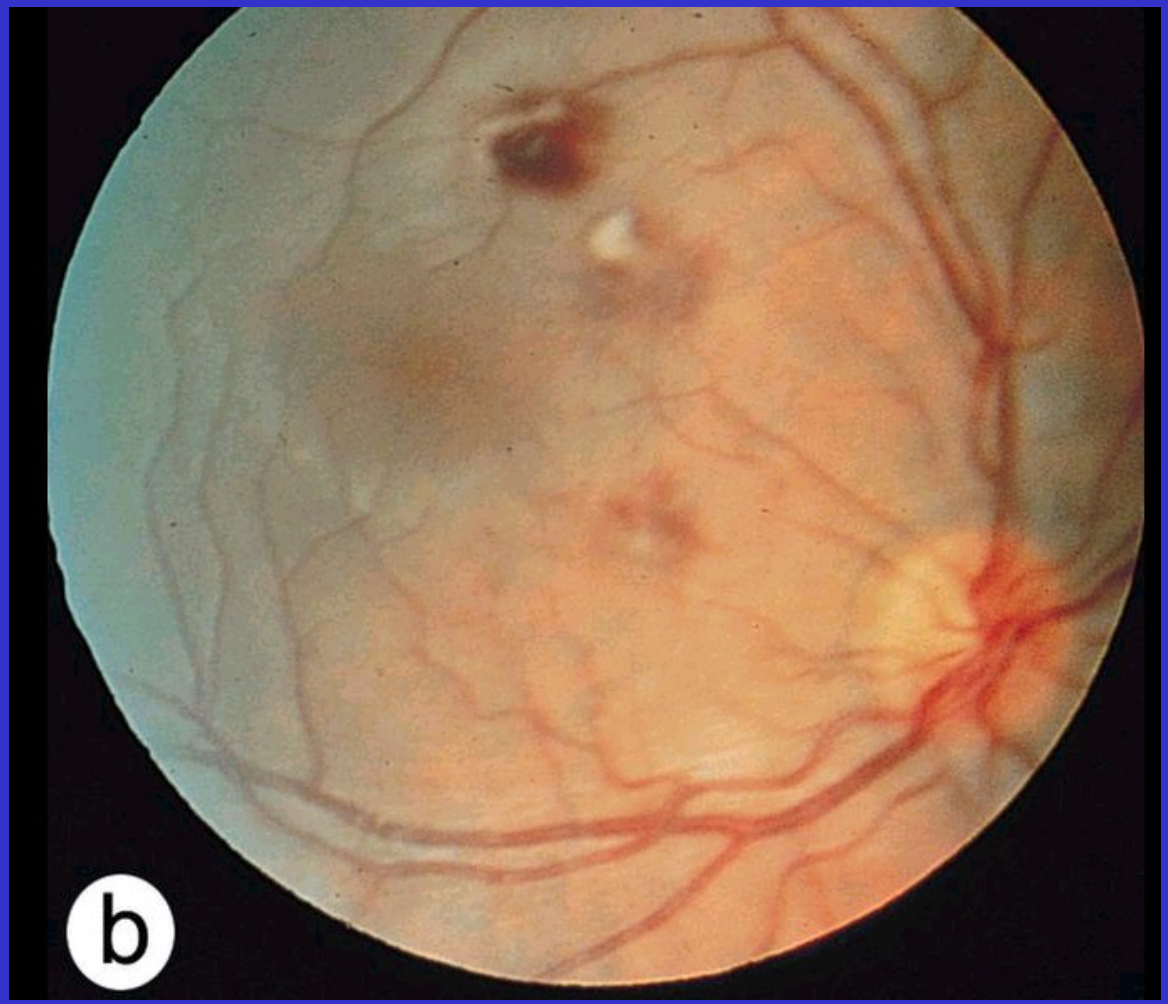


Chiazze di Janeway



Petecchie congiuntivali

Emboli settici della retina



Esami di laboratorio

- **Evidenza di infezione/infiammazione**
  - **VES elevata**
  - **Leucocitosi**
  - **Anemia**
  - **Proteina C reattiva**
- **Evidenza di formazione di immunocomplessi**
  - **Elevate globuline sieriche**
  - **Fattore reumatoide**
  - **Anticorpi antinucleo**
  - **Ipocomplementemia**
- **Evidenza di coinvolgimento renale**
  - **Ematuria**
  - **Proteinuria**

COMPLICANZE

- Embolie
- Scompenso cardiaco congestizio
  - EI aortica, anziani, inizio terapia antibiotica tardiva
- Ascessi miocardici
- Emorragie secondarie a rottura di aneurismi
  - embolie vasa vasorum, emorragie cerebrali
- Insufficienza renale
- Recidive TD

Current Infectious Disease Reports
November 2017, 19:41 | Cite as

Neurologic Complications of Infective Endocarditis: Recent Findings

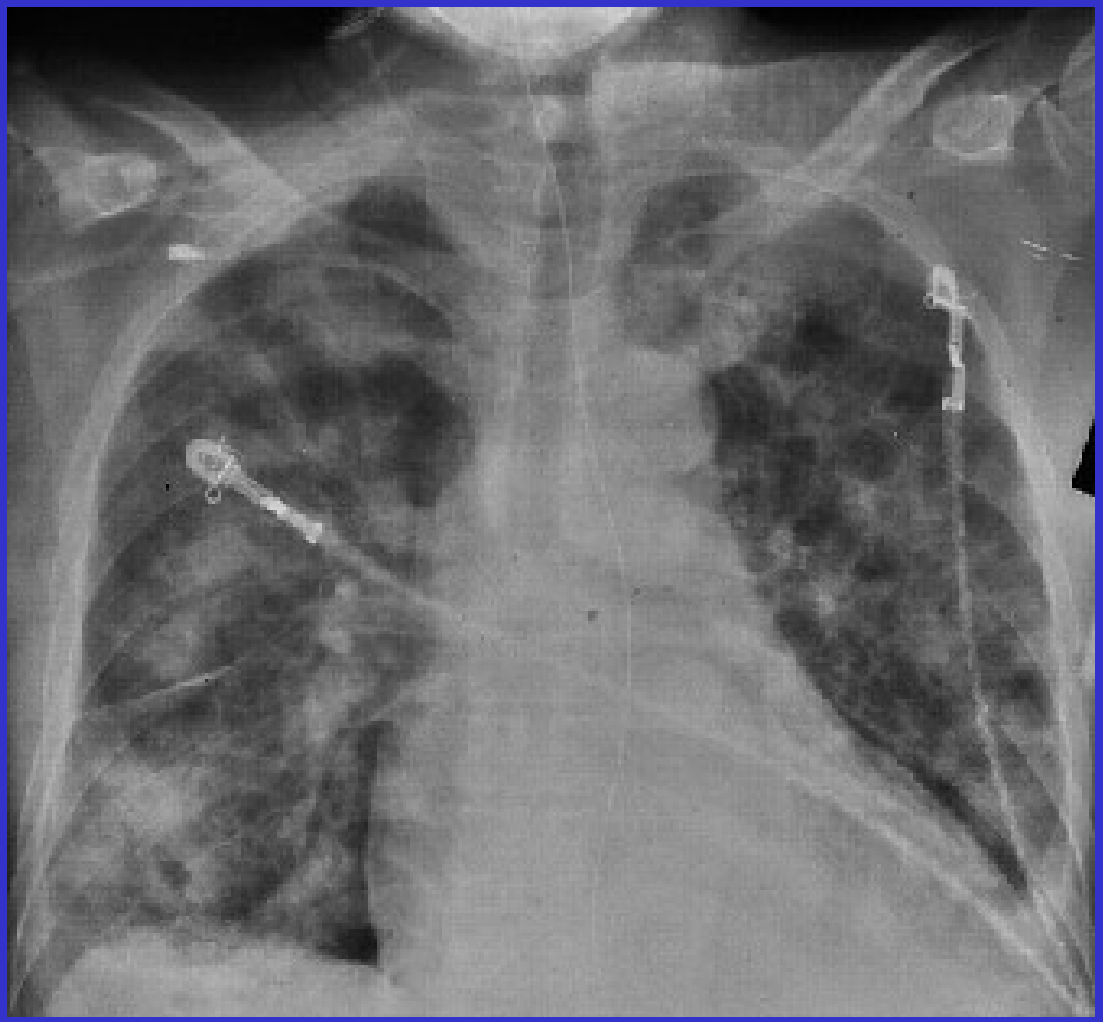
Authors | Authors and affiliations

Marie Cantier, Mikael Mazighi, Isabelle Klein, J. P. Desilles, Michel Wolff, J. F. Timsit, Romain Sonneville

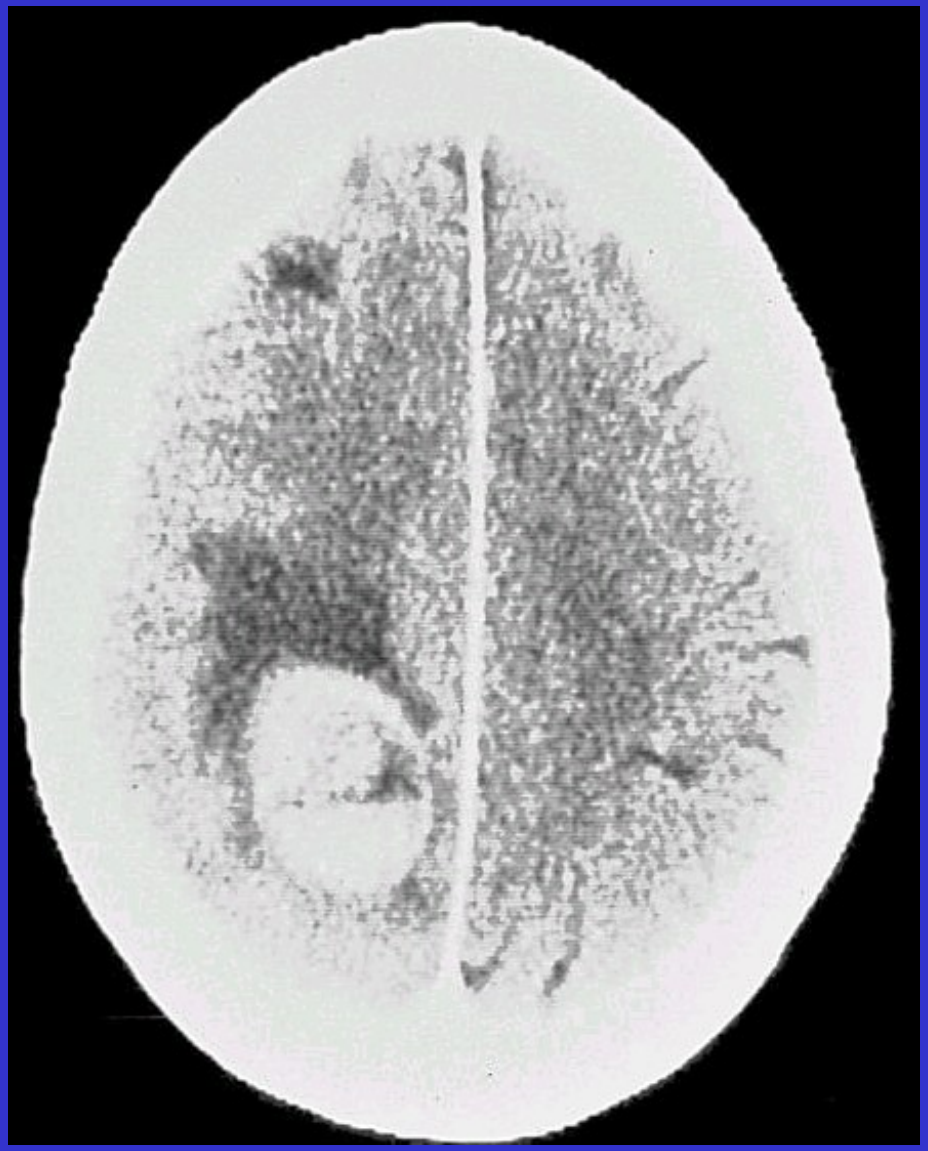
Central Nervous System Infections (K Bloch, Section Editor)
First Online: 19 September 2017

462
Downloads

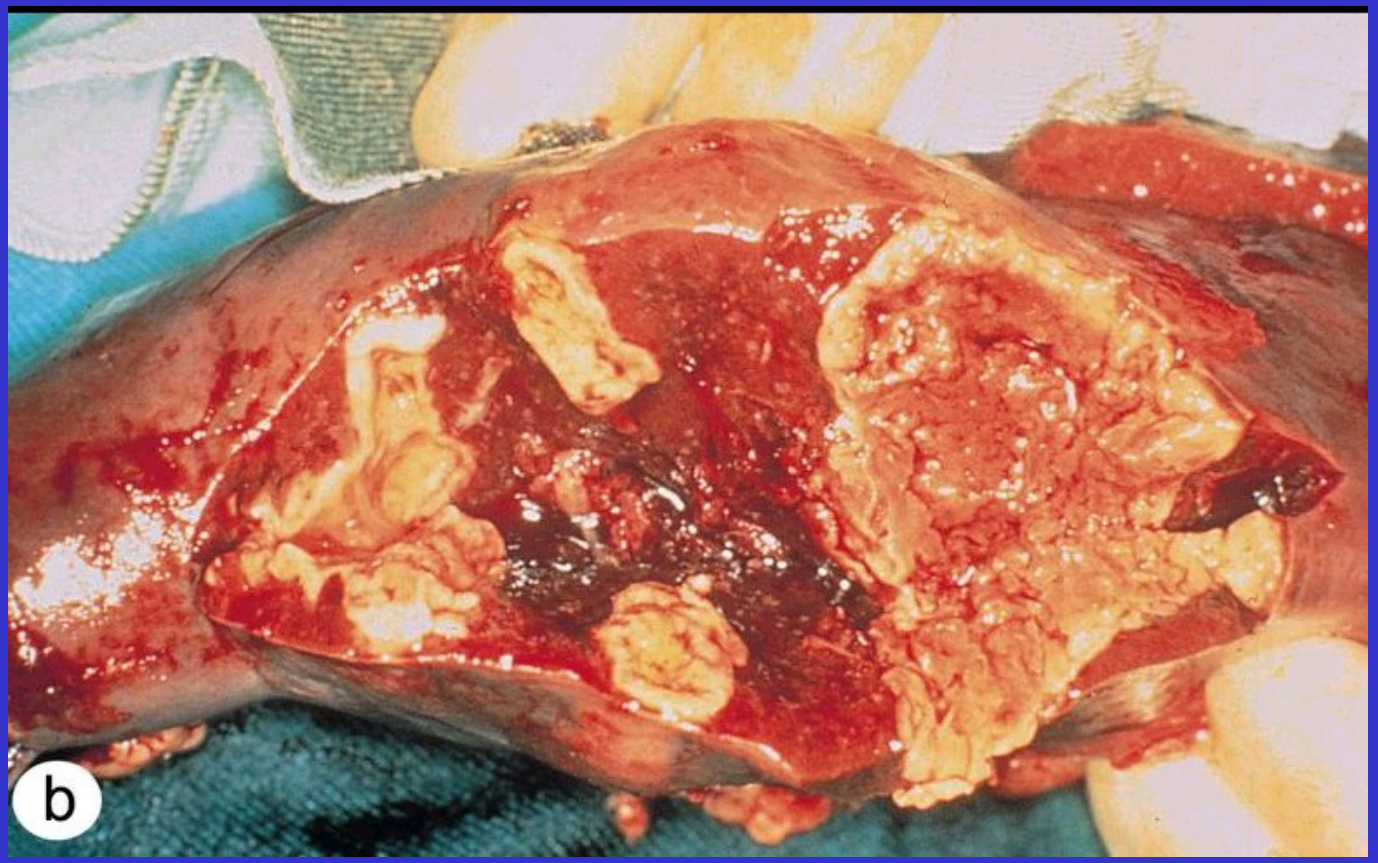
Emboli settici polmonari



Ascesso cerebrale



Ascessi multipli splenici



Condizioni con rischio elevato di complicazioni in corso di EI

- Valvole cardiache protesiche
- EI sinistra
- EI da *S. aureus*
- EI micotica
- Pregressa EI
- Sintomi clinici prolungati (>3 mesi)
- Cardiopatia congenita cianotica
- Pazienti con shunt sistemico-polmonari
- Scarsa risposta clinica alla terapia antimicrobica

Endocardite mitralica: rischio di emboli

Localizzazione	Rischio
Valvola mitralica	25%
Coinvolgimento AMVL	40%
AMVL e dimensione vegetazione > 10 mm	60%
AMVL e dimensione vegetazione > 10 mm e mobile	60%-80%

AMVL = lembo anteriore valvola mitralica

DIAGNOSI

- **Febbre da più di 8-10 giorni**
- **Cardiopatia pregressa**
- **Splenomegalia**
- **Ematuria microscopica**
- **Anemia**
- **Segni cutanei**

- **Emocoltura (batteriemia continua)**

Soggetti a rischio di Endocardite infettiva

I gruppi di **soggetti ad alto rischio di IE**
- Pazienti con pregressa IE.
- Pazienti con valvole protesiche impiantate chirurgicamente, con valvole protesiche impiantate transcatetere e con qualsiasi materiale utilizzato per la riparazione delle valvole cardiache.
- I pazienti con cardiopatie congenite (CHD)
- Pazienti con dispositivi di assistenza ventricolare

I pazienti **a rischio intermedio di IE**:
(i) cardiopatia reumatica (RHD);
(ii) malattia valvolare degenerativa non reumatica;
(iii) anomalie valvolari congenite, compresa la malattia della valvola aortica bicuspide;
(iv) dispositivi elettronici cardiovascolari impiantati (CIED);
(v) cardiomiopatia ipertrofica

CRITERI DI DUKE

The 2023 Duke-ISCVID IE Criteria (Major)

Proposed Changes in Bold Type

Major	
Microbiologic	(1) Positive blood cultures **i. Microorganisms that commonly cause IE isolated from two or more separate blood culture sets** or ii. Microorganisms that occasionally or rarely cause IE **isolated from three or more separate blood culture sets** (2) Positive laboratory tests **i. Positive PCR or other nucleic acid-based technique for *Coxiella burnetii, Bartonella species, or Tropheryma whipplei* from blood** or *ii. Coxiella burnetii* antiphase I IgG antibody titer > 1:800, or isolated from a single blood culture or **iii. Indirect immunofluorescence assays (IFA) for detection of IgM and IgG antibodies to *Bartonella henselae* or *Bartonella quintana* with IgG titer > 1:800**
Imaging	(1) Echocardiography and **Cardiac Computed Tomography** Imaging I. Echocardiography and/or **Cardiac CT** showing vegetation, valvular/leaflet perforation, valvular/leaflet aneurysm, abscess, pseudoaneurysm, or intracardiac fistula or II. Significant new valvular regurgitation on echocardiography as compared to previous imaging. Worsening or changing of pre-existing regurgitation is not sufficient. or III. New partial dehiscence of prosthetic valve as compared to previous imaging (2) **[18F]FDG PET/CT Imaging** **Abnormal metabolic activity involving a native or prosthetic valve, ascending aortic graft (with concomitant evidence of valve involvement), intracardiac device leads or other prosthetic material**
Surgical	**Evidence of IE documented by direct inspection during heart surgery neither Major Imaging Criteria nor subsequent histologic or microbiologic confirmation**

Please note significant changes, including new microbiology diagnostics, imaging, and inclusion of surgical inspection as a new Major Clinical Criterion.

Clinical Infectious Diseases, 04 May 2023
https://doi.org/10.1093/cid/ciad271

The 2023 Duke-ISCVID IE Criteria (Minor)

Proposed Changes in Bold Type

Minor	
Predisposition	- **Previous history of IE** - Prosthetic valve - Previous valve repair - Congenital heart disease - More than mild regurgitation or stenosis of any etiology - **Endovascular CIED** - Hypertrophic obstructive cardiomyopathy - Injection drug use
Fever	Documented temperature greater than 38.0 degrees Centigrade (100.4 degrees Fahrenheit)
Vascular Phenomena	Clinical or radiological evidence of arterial emboli, septic pulmonary infarcts, **cerebral or splenic abscess**, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions, purulent purpura
Immunologic Phenomena	Positive rheumatoid factor, Osler's nodes, Roth's spots, or immune complex-mediated glomerulonephritis
Microbiologic Evidence, Falling Short of a Major Criterion	1) Positive blood cultures for a microorganism consistent with IE but not meeting the requirements for Major Criterion **2) Positive culture, PCR or other nucleic acid based test (amplicon or shotgun sequencing, in situ hybridization) for an organism consistent with IE from a sterile body site other than cardiac tissue, cardiac prosthesis, or embolus; or a single finding of a skin bacterium by PCR on a valve or wire without additional clinical or microbiological supporting evidence**
Imaging	**Abnormal metabolic activity as detected by [18F]FDG PET/CT within 3 months of implantation of prosthetic valve, ascending aortic graft (with concomitant evidence of valve involvement), intracardiac device leads or other prosthetic material**
Physical Examination	New valvular regurgitation identified on auscultation, if echocardiography is not available. Worsening or changing of pre-existing murmur not sufficient

Please note additional predisposing conditions (transcatheter valve implants, endovascular cardiac implantable electronic devices, prior IE) were clarified.

Clinical Infectious Diseases, 04 May 2023
https://doi.org/10.1093/cid/ciad271

Infective Endocarditis: *Modified Duke Criteria*

MAJOR CRITERIA	minor criteria
1. Blood cultures positive for infective endocarditis	1. Predisposing factor [a]
2. Evidence of endocardial involvement	2. Temperature >38°C
	3. Vascular phenomena [b]
	4. Immunologic phenomena [c]
	5. Microbiologic evidence [d]

[a] Intravenous drug use or a predisposing heart condition.

[b] Vascular phenomena include major arterial emboli, septic emboli, pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhage, and painless skin lesions (i.e., janeway lesions).

[c] Immunologic phenomena include glomerulonephritis, painful nodes (i.e., Osler's nodes), retinal haemorrhages with small, clear centers (i.e., Roth's spots), and positive rheumatoid factor.

[d] Positive blood culture not meeting a major criterion or serologic evidence of an active infection with an organism known to cause infective endocarditis

Two major criteria
or
One major and three minor criteria
or
Five minor criteria

Definite Diagnosis

One major and one minor criteria
or
Three minor criteria

Possible Diagnosis

Diagnosi

Table 14 Definitions of the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis

Major criteria

1. Blood cultures positive for IE

a. Typical microorganisms consistent with IE from 2 separate blood cultures:
- *Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus*; or
- Community-acquired enterococci, in the absence of a primary focus; or

b. Microorganisms consistent with IE from persistently positive blood cultures:
- ≥2 positive blood cultures of blood samples drawn >12 h apart; or
- All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or

c. Single positive blood culture for Coxiella burnetii or phase 1 IgG antibody titre >1:800

2. Imaging positive for IE

a. Echocardiogram positive for IE:
- Vegetation;
- Abscess, pseudoaneurysm, intracardiac fistula;
- Valvular perforation or aneurysm;
- New partial dehiscence of prosthetic valve.

b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.

c. Definite paravalvular lesions by cardiac CT.

Minor criteria

1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever defined as temperature >38°C.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

Table 13 Definition of infective endocarditis according to the modified Duke criteria (adapted from Li et *al.*[87])

Definite IE

Pathological criteria
- Microorganisms demonstrated by culture or on histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
- Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis

Clinical criteria
- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

Possible IE
- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

Rejected IE
- Firm alternate diagnosis; or
- Resolution of symptoms suggesting IE with antibiotic therapy for ≤4 days; or
- No pathological evidence of IE at surgery or autopsy, with antibiotic therapy for ≤4 days; or
- Does not meet criteria for possible IE, as above

ECOCARDIOGRAFIA

- **Ecocardiografia transtoracica (TTE)**
  - **Specificità: 98%**
  - **Sensibilità: 60% in NVE; solo 20% in PVE**
    - **Obesità, deformazioni toraciche, BCPO**
  - **Inadeguata nel rilevare complicazioni: sensibilità 28-40%**
  - **Può escludere la diagnosi in pazienti a basso rischio di EI**

ECOCARDIOGRAFIA

– **Ecocardiografia transesofagea (TEE)**

- **Sensibilità e specificità: 90-98%**
- **Utile in PVE e nelle complicazioni (ascessi)**
- **Raccomandata in pazienti a rischio intermedio o elevato di EI con TTE normale**
- **Valore predittivo negativo: >92%**

Ecocardiografia
Quesiti

- **E' necessaria in tutti i pazienti con EI sospetta?**
- **Quando è sufficiente la TTE o è necessaria la TEE nella diagnosi iniziale?**
- **Entrambe le tecniche vanno fatte in tutti i pazienti?**
- **Quale tecnica ha il miglior costo/efficacia**

TTE/TOE

2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

Sensibilità

TTE. 70% nativa, 50% protesica
TOE. 96% nativa, 92% protesica

Specificità

TTE/TOE. 90%

In case of persistent clinical suspicion of IE and an initially negative examination, repeat TTE/TOE must be performed 5-7 days; later, if the clinical level of suspicion is still high, or even earlier in the case of *S. aureus* infection.

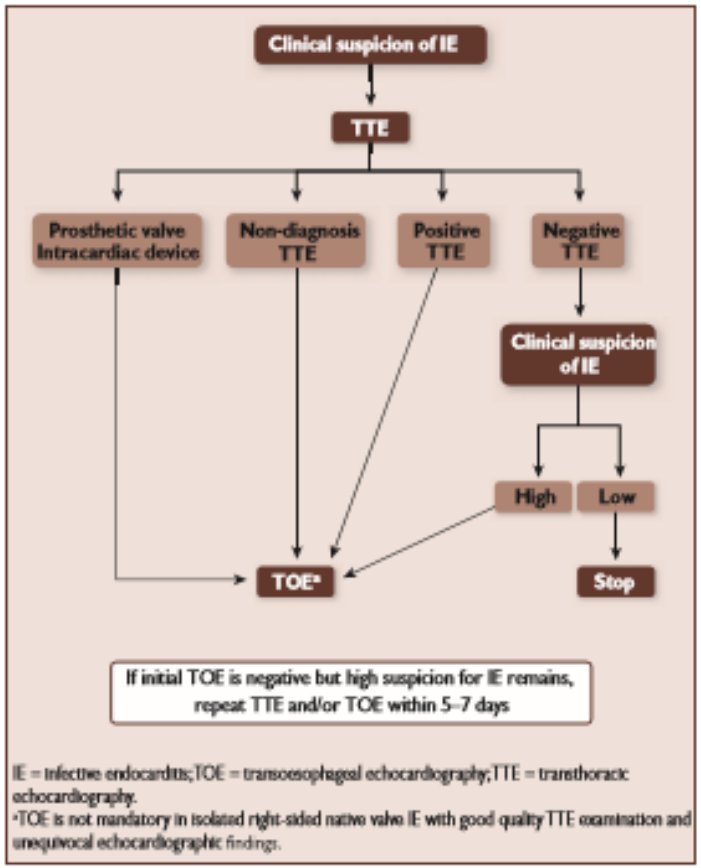


Figure 1 Indications for echocardiography in suspected infective endocarditis.

Le linee guida propongono l'aggiunta tra i criteri diagnostici maggiori di:

1. Imaging nucleare per la diagnosi su valvola protesica: ^{18} FDG PET/TC e SPECT/TC con leucociti marcati con ^{99m} Tc. La PET/TC non va usata se la valvola è stata impiantata da <3 mesi (possibili falsi positivi da modifiche infiammatorie post-chirurgiche). Ruoli futuri: valutazione su device impiantati, riscontro di emboli settici. La SPECT/TC è più sensibile e da preferire se possibile.
2. Lesioni paravalvolari individuate alla cardio-TC. L'accuratezza è simile all'ecocardiogramma transesofageo, soprattutto nel definire l'anatomia nell'EI aortica; aiuta nel planning chirurgico.

Queste modifiche dei criteri maggiori di Duke non sono condivise dalle linee guida dell'American Heart Association 2015

Imaging

Table 14 Definitions of the terms used in the European Society of Cardiology 2015 modified criteria for the diagnosis of infective endocarditis

Major criteria

1. Blood cultures positive for IE

a. Typical microorganisms consistent with IE from 2 separate blood cultures:
- *Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus*; or
- Community-acquired enterococci, in the absence of a primary focus; or

b. Microorganisms consistent with IE from persistently positive blood cultures:
- ≥2 positive blood cultures of blood samples drawn >12 h apart; or
- All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or

c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800

2. Imaging positive for IE

a. Echocardiogram positive for IE:
- Vegetation;
- Abscess, pseudoaneurysm, intracardiac fistula
- Valvular perforation or aneurysm;
- New partial dehiscence of prosthetic valve.

b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocytes SPECT/CT.

c. Definite paravalvular lesions by cardiac CT.

Minor criteria

1. Predisposition such as predisposing heart condition, or injection drug use.
2. Fever defined as temperature >38°C.
3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway's lesions.
4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

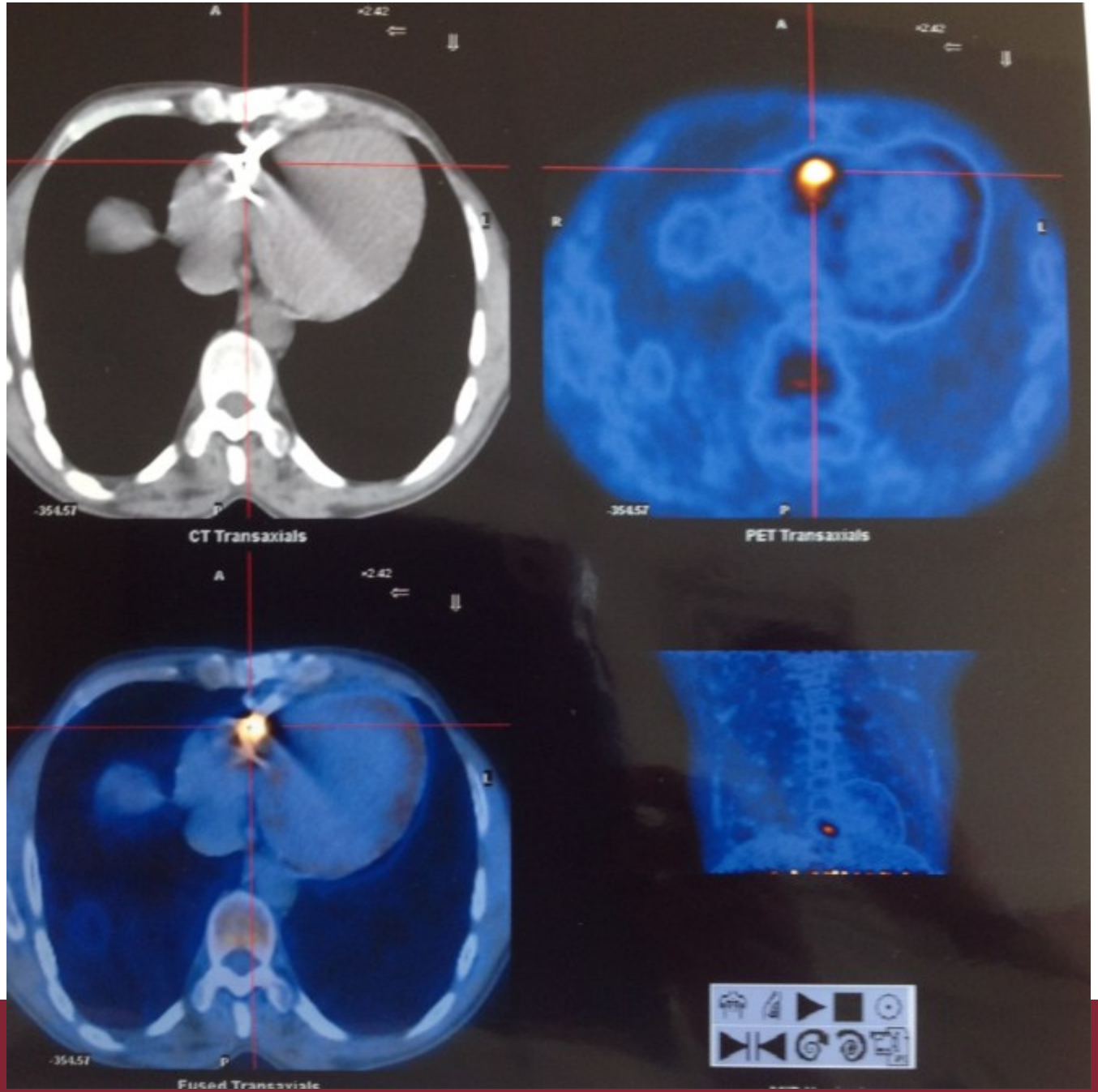
2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

✓**reduction in the rate of misdiagnosed IE, classified in the 'Possible IE' category using the Duke criteria (PVE)**

✓**detection of peripheral embolic and metastatic infectious events.**

SPECT	PET
Radiolabelled leucocytes	18F-FDG
Highest sensitivity in the acute phase	increases the sensitivity of the modified Duke criteria at admission from 70 to 97%
More specific for IE and infectious foci	Less specific for IE (thrombi, atherosclerotic plaques, vasculitis, tumors, post-surgical inflammation)
Lower spatial resolution	Better spatial resolution
More time consuming	Single acquisition time point
	High uptake in the brain cortex (septic emboli)


CT Transaxials
PET Transaxials
Fused Transaxials

Mortalità per EI in relazione ad agente eziologico

Microrganismo	% mortalità
Strept. viridans e *bovis*	4-16
Enterococco	15-25
S. aureus	25-47
Coxiella burnetii	5-37
P. aeruginosa, enterobatteri e miceti	>50

Decorso dell'endocardite da *S. aureus* in TD

	VANCO N=39	β-lattamine N= 45	*P*
Mortalità (%)[a]	13 (33.3)	4 (8.9)	0.005
Fallimento clinico g. 7 (%)	23 (65.7)	19 (45.2)	0.07
Complicazioni	31 (68.9)	32 (82.1)	0.2
Giorni di batteriemia[a,b]	5 [1-16]	3.5 [1-20]	0.02
Giorni di febbre[b]	7.5 [0-29]	5.0 [0-16]	0.1

[a] $P<0.05$, [b] mediana [range]

Lodise TP, ICAAC 2002

PROGNOSI

- **Mortalità per NVE e PVE: 20-50% (scompenso cardiaco, emboli cerebrali)**
- **Fattori prognostici:**
  - **Età**
  - **Agente eziologico**
  - **Complicazioni (ascessi)**
  - **Patologie concomitanti (insufficienza cardiaca, insufficienza renale, eventi neurologici, immunodepressione)**

Cardio-TC

Major criteria

1. Blood cultures positive for IE

a. Typical microorganisms consistent with IE from 2 separate blood cultures:
- *Viridans streptococci, Streptococcus gallolyticus (Streptococcus bovis), HACEK group, Staphylococcus aureus*; or
- Community-acquired enterococci, in the absence of a primary focus; or

b. Microorganisms consistent with IE from persistently positive blood cultures:
- ≥2 positive blood cultures of blood samples drawn >12 h apart; or
- All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart); or

c. Single positive blood culture for Coxiella burnetii or phase I IgG antibody titre >1:800

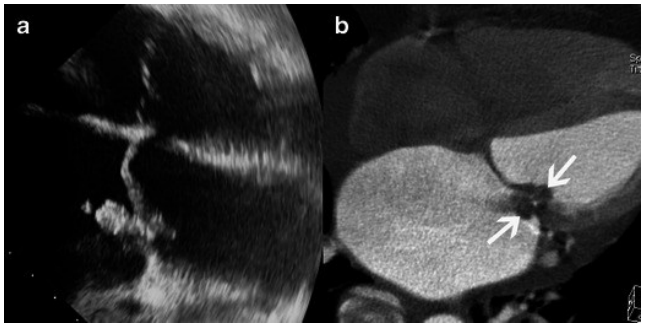
2. Imaging positive for IE

a. Echocardiogram positive for IE:
- Vegetation;
- Abscess, pseudoaneurysm, intracardiac fistula;
- Valvular perforation or aneurysm;
- New partial dehiscence of prosthetic valve.

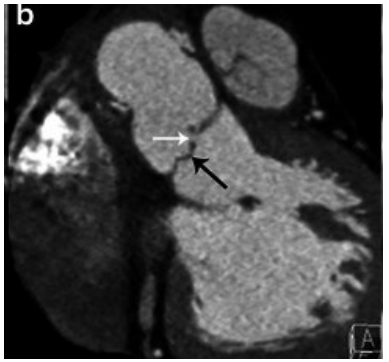
b. Abnormal activity around the site of prosthetic valve implantation detected by ^{18}F-FDG PET/CT (only if the prosthesis was implanted for >3 months) or radiolabelled leukocyte SPECT/CT.

c. Definite paravalvular lesions by cardiac CT.

- **abscess/pseudoaneurysm accuracy similar to TOE**
- **superior for any perivalvular extension**
- **in aortic IE additional data on the size, anatomy and calcification of the aortic valve, root and ascending aorta calcification of the aorta (surgical planning)**
- **in right-sided endocarditis, useful to study concomitant pulmonary disease**
- **Prostetic valve large compartive studies between TOE and MSCT are missing**



Four-chamber views in the TEE study (a) and MSCT acquisitions with MPR reconstruction (b). Large vegetation (*white arrow*) and destruction of the mitral valve with substantial dilatation of the left atrium and pericardial effusion



Aortic valve infective endocarditis – Coronal oblique view
Perforation (*white arrow*) and valvular aneurysms(*black arrow*)

Grob, A., Thuny, F., Villacampa, C., Flavian, A., Gaubert, J. Y., Raoult, D., ... & Jacquier, A. (2014). Cardiac multidetector computed tomography in infective endocarditis: a pictorial essay. *Insights into imaging*, *5*(5), 559-570.

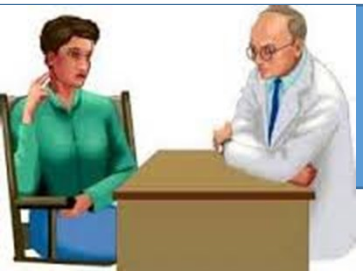
TERAPIA MEDICA

- **Terapia antibiotica**
  - **azione battericida**
  - **capacità di penetrazione**
  - **inizio precoce**
  - **via endovenosa**
  - **dosaggi elevati**
  - **durata prolungata (4-8 settimane)**

JAMA. 1995;274:1706–1713
N Engl J Med 2001;345:1318-1330.

Terapia antibiotica – principi generali

- Usare farmaci battericidi
- Precoce consulenza cardiochirurgica in tutti i casi in cui è presente o prevedibile una complicanza
- Durata: 2-6 settimane. I regimi “brevi” sono raccomandati solo in un piccolo numero di pazienti accuratamente selezionati con EI del cuore dx, oppure da Streptococchi viridanti altamente suscettibili e terapia combinata.



Altro caso clinico

-Paziente di 54 aa, in APR diagnosi di gammapatia monoclonale circa 2 aa prima, intervento di sostituzione valvolare mitralica con protesi biologica a Gennaio 2016

-Il 7/10 viene ricoverato presso altro nosocomio per effettuare accertamenti di approfondimento per il riscontro ad esami ematochimici di controllo di anemia normocromica normocitica con valori di Hb di circa 8 g/dl

-Dopo 3 giorni dall'ingresso in reparto comparsa di febbre con cuspidi a 41°C associata a brivido e riscontro agli esami ematochimici di alterazioni compatibili con iniziale stato settico.

Viene effettuato ecocardiogramma TT con riscontro di piccola immagine di plus a livello della valvola mitralica biologica. Il paziente viene successivamente trasferito nel nostro reparto di Malattie Infettive in data 12/10

Iter diagnostico terapeutico

-**Esame clinico**: il paziente all'ingresso si presenta dispnoico, tachipnoico, T.C. fino a 39°C, obiettivamente ACR soffio sistolico 2/6 Levine sul focolaio della mitrale; al torace presenza di rumori umidi medio-basali bilaterali, moderato turgore giugulare. Considerato il quadro di scompenso cardiaco viene impostata terapia con diuretici e beta bloccanti con miglioramento clinico.

-**Esami ematochimici**: leucocitosi neutrofila, spiccato aumento degli indici di flogosi, anemia normocromica normocitica piastrinopenia severa(PLT 22000/mmc), iperbilirubinemia(3 mg/dl) prevalentemente indiretta(SOFA score 7)

-**Esami microbiologici: Emocolture positive per *S. aureus meticillino-resistente*.**

-**Esami strumentali**:

- ✓ **Ecocardiogramma TE conferma la presenza di vegetazione di 0,2 x 0,6 cm sulla protesi biologica con insufficienza mitralica di lieve- moderata entità,**
- ✓ **HRTC: addensamento a livello del lobo inferiore sx con versamento basale bilaterale**

-Approccio terapeutico: Impostata tp antibiotica empirica con Vancomicina e Gentamicina e successivamente con Daptomicina(10 mg/kg)

Nel corso della degenza…

-Nei primi 4 giorni di terapia antibiotica persistenza di stato settico ed emocolture persistentemente positive seppur con paziente emodinamicamente stabile

- Vien ripetuto ecocardiogramma TE che mostra comparsa di **nuove vegetazioni** lungo tutto l'anello valvolare mitralico e incremento dimensionale della precedente vegetazione con dimensioni pari a **0,6 x 1 cm.**

Cardiochirurgo si… o no??
Inizia Ping-Pong

- **Viene proseguita la terapia antibiotica in atto con progressiva riduzione della leucocitosi neutrofila e degli indici di flogosi, scomparsa della febbre e negativizzazione delle emocolture(ultime emocolture positive del 24/10)**

- **Viene ripetuto ecocardiogramma TE in data 08/11. L'esame mostra scomparsa di gran parte delle vegetazioni precedentemente segnalate e riduzione dimensionale della vegetazione più grande ora di circa 0,4 x 0,6 cm, lieve rigurgito mitralico.**

- **Dopo consulenza CCH, si decide soltanto di proseguire con terapia medica e posticipare un eventuale intervento di sostituzione valvolare**.

Il decorso improvvisamente si complica…

-Il 16/11 il paziente presenta nuovamente un episodio di scompenso cardiaco con dispnea tachipnea e reperto toracico compatibile con EPA. Riscontro ECGgrafico di flutter a conduzione variabile alla F.C. di circa 150 bpm. Per ricomparsa della febbre con leucocitosi neutrofila viene effettuata una Rx torace che mostra esteso addensamento in sede medio-basale dx

-Il giorno successivo il paziente presenta nuovamente dispnea e tachipnea non responsiva a terapia medica e nuovo aumento della F.C. fino a 140 bmp con persistenza del flutter atriale a conduzione variabile. Compare ipotensione ingravescente e segni di shock cardiogeno con deterioramento del sensorio

-**Viene richiesto consulenza rianimatoria e cardiologica. Un ecocardiogramma TT effettuato nel sospetto di embolia polmonare acuta mostra la presenza di completa deiscenza valvolare. Il paziente viene pertanto operato in emergenza per sostituzione valvolare**

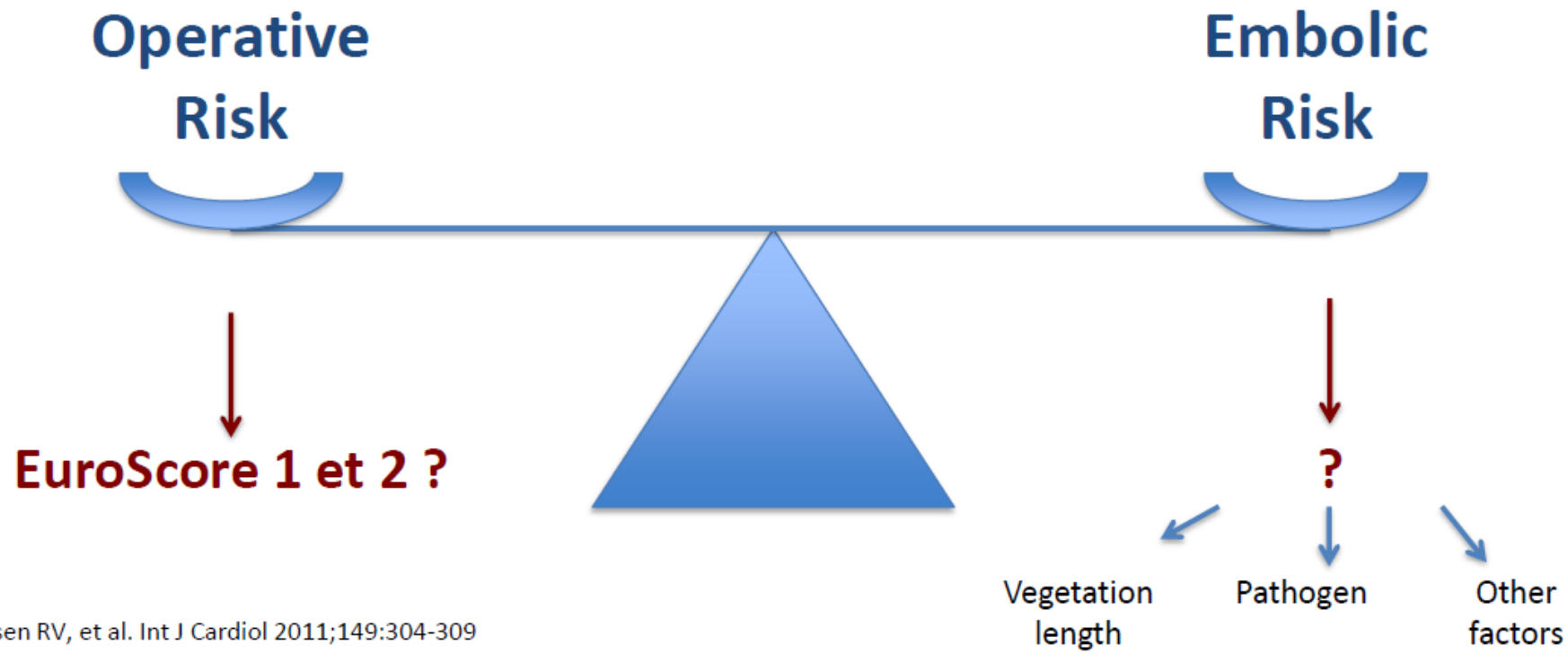
Trattamento chirurgico

Indicazioni

- Insufficienza cardiaca dovuta a disfunzione valvolare
- Invasione miocardica - ascessi
- Patogeni resistenti
  - Funghi
  - Bacilli gram-negativi
  - Enterococchi multi-resistenti
- Recidiva di PVE
- Endocardite sinistra da *S. aureus*
- Endocardite su valvola protesica da *S. aureus*
- Alto rischio di complicazioni emboliche
- Endocarditi ad emocoltura negativa non responsive a terapia antimicrobica

ACC/AHA Circulation 1998;98:1949-84

Quantification of Benefit/Risk Ratio for surgery must be evaluated



Rasmussen RV, et al. Int J Cardiol 2011;149:304-309

Infection (2017) 45:413–423
DOI 10.1007/s15010-016-0977-9

ORIGINAL PAPER

A risk factor analysis for in-hospital mortality after surgery for infective endocarditis and a proposal of a new predictive scoring system

Giuseppe Gatti[1,3] · Bernardo Benussi[1] · Florida Gripshi[1] · Alessio Della Mattia[1] · Alberto Proclemer[1] · Antonio Cannatà[1] · Lorella Dreas[1] · Roberto Luzzati[2] · Gianfranco Sinagra[1] · Aniello Pappalardo[1]

Vlahakes GJ
«Consensus guidelines for the surgical treatment of infective endocarditis»: the surgeon must lead the team
J Thorac Cardiovasc Surg 2017;153:1259-1260

For IE, a surgeon-lead team multidisciplinary team is needed...

… Many patients with IE are in between, however, requiring more critical judgement that can only be provided by a surgeon-led team.

… The responsible surgeon should be present when transesophageal echocardiography is performed di patients with IE
.Particularly in patients with previous cardiac valvular surgery, echocardiographic findings must be made with knowledge of the anatomy and details from the previous operation…

Indications for surgery	Timing[a]	Class[b]	Level[c]	Ref.[d]
1. Heart failure				
Aortic or mitral NVE or PVE with severe acute regurgitation, obstruction or fistula causing refractory pulmonary oedema or cardiogenic shock	Emergency	I	B	111,115, 213,216
Aortic or mitral NVE or PVE with severe regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance	Urgent	I	B	37,115, 209,216, 220,221
2. Uncontrolled infection				
Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)	Urgent	I	B	37,209, 216
Infection caused by fungi or multiresistant organisms	Urgent/ elective	I	C	
Persisting positive blood cultures despite appropriate antibiotic therapy and adequate control of septic metastatic foci	Urgent	IIa	B	123
PVE caused by staphylococci or non-HACEK gram-negative bacteria	Urgent/ elective	IIa	C	
3. Prevention of embolism				
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent	I	B	9,58,72, 113,222
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	Urgent	IIa	B	9
Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm)	Urgent	IIa	B	113
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery[e]	Urgent	IIb	C	

Anticoagulanti/antiaggreganti

Eur J Clin Microbiol Infect Dis. 2011 Feb;30(2):151-7. doi: 10.1007/s10096-010-1063-3. Epub 2010 Sep 21.

Warfarin therapy and incidence of cerebrovascular complications in left-sided native valve endocarditis.

Snygg-Martin U[1], Rasmussen RV, Hassager C, Bruun NE, Andersson R, Olaison L.

…with only three on warfarin. CVC were significantly less frequent in patients on warfarin (6% vs. 26%, odds ratio [OR] 0.20, 95% confidence interval [CI] 0.06-0.6, p = 0.006). No increase in haemorrhagic lesions was detected in patients on warfarin. Staphylococcus aureus aetiology (adjusted OR [aOR] 6.3, 95% CI 3.8-10.4) and vegetation length (aOR 1.04, 96% CI 1.01-1.07)…

March 8, 1999

Infective Endocarditis Due to Staphylococcus aureus

Deleterious Effect of Anticoagulant Therapy

Pilar Tornos, MD; Benito Almirante, MD; Sonia Mirabet, MD; et al

Conclusions Our results suggest that in left-sided *S aureus* IE anticoagulant therapy is closely associated with death due to neurologic damage. According to our data, as soon as the clinical diagnosis of *S aureus* IE is indicated the use of anticoagulant therapy should be immediately stopped until the septic phase of the disease is overcome.

Basic Science Reports

Acetylsalicylic Acid Reduces Vegetation Bacterial Density, Hematogenous Bacterial Dissemination, and Frequency of Embolic Events in Experimental *Staphylococcus aureus* Endocarditis Through Antiplatelet and Antibacterial Effects

Leon Iri Kupferwasser, MD; Michael R. Yeaman, PhD; Shelley M. Shapiro, MD, PhD; Cynthia C. Nast, MD; Paul M. Sullam, MD; Scott G. Filler, MD; Arnold S. Bayer, MD

Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 42, No. 5, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(03)00829-5

CLINICAL RESEARCH **Clinical Trials**

A Randomized Trial of Aspirin on the Risk of Embolic Events in Patients With Infective Endocarditis

Kwan-Leung Chan, MD, FRCPC, FACC,* Jean G. Dumesnil, MD, FRCPC,†
Bibiana Cujec, MD, FRCPC,‡ Anthony J. Sanfilippo, MD, FRCPC,§ John Jue, MD, FRCPC,‖
Michele A. Turek, MD, FRCPC,* Trevor I. Robinson, MD,¶ David Moher, MSc,* for the Investigators of the Multicenter Aspirin Study in Infective Endocarditis

CONCLUSIONS In endocarditis patients already receiving antibiotic treatment, the addition of aspirin does not appear to reduce the risk of embolic events and is likely associated with an increased risk of bleeding. Aspirin is not indicated in the early management of patients with IE. (J Am Coll

Anticoagulanti/antiaggreganti

2015 ESC Guidelines for the management of infective endocarditis

The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC)

The recommendations for management of anticoagulant therapy in IE patients are based on a low level of evidence, and decisions should be made on an individual basis by the Endocarditis Team. The role of bridging therapy with unfractionated or low molecular weight heparin has not been studied in patients with IE, but may have reasonable advantages in special situations (i.e. in unstable patients) before surgical decisions are made or to avoid drug interactions.

Evidence does not support initiation of antiplatelet therapy in patients diagnosed with IE,[258] despite promising results in experimental studies.[468] Some cohort studies indicate a possible reduction in the rate of embolic complications[257] or IE development in subgroups of patients already on antiplatelet therapy,[469] but the data are contradictory.[470,471]

Endocarditis Team - ESC -

- **When to refer a patient**
- **Characteristics of the reference centre**
- **Role of the «endocarditis team»**

Table 8 Characteristics of the 'Endocarditis Team'

When to refer a patient with IE to an 'Endocarditis Team' in a reference centre 1. Patients with complicated IE (i.e. endocarditis with HF, abscess, or embolic or neurological complication or CHD), should be referred early and managed in a reference centre with immediate surgical facilities. 2. Patients with non-complicated IE can be initially managed in a non-reference centre, but with regular communication with the reference centre, consultations with the multidisciplinary 'Endocarditis Team', and, when needed, with external visit to the reference centre.
Characteristics of the reference centre 1. Immediate access to diagnostic procedures should be possible, including TTE, TOE, multislice CT, MRI, and nuclear imaging. 2. Immediate access to cardiac surgery should be possible during the early stage of the disease, particularly in case of complicated IE (HF, abscess, large vegetation, neurological, and embolic complications). 3. Several specialists should be present on site (the 'Endocarditis Team'), including at least cardiac surgeons, cardiologists, anaesthesiologists, ID specialists, microbiologists and, when available, specialists in valve diseases, CHD, pacemaker extraction, echocardiography and other cardiac imaging techniques, neurologists, and facilities for neurosurgery and interventional neuroradiology.
Role of the 'Endocarditis Team' 1. The 'Endocarditis Team' should have meetings on a regular basis in order to discuss cases, take surgical decisions, and define the type of follow-up. 2. The 'Endocarditis Team' chooses the type, duration, and mode of follow up of antibiotic therapy, according to a standardized protocol, following the current guidelines. 3. The 'Endocarditis Team' should participate in national or international registries, publicly report the mortality and morbidity of their centre, and be involved in a quality improvement programme, as well as in a patient education programme. 4. The follow-up should be organized on an outpatient visit basis at a frequency depending on the patient's clinical status (ideally at 1, 3, 6, and 12 months after hospital discharge, since the majority of events occur during this period[57]).

Prevenzione dell'endocardite infettiva

- Identificazione pazienti a rischio moderato-elevato
- Immediata terapia di qualsiasi infezione
- Rigoroso attenzione alle cure dentali
- Antibiotico-profilassi durante procedure che possono causare batteriemia

Restrizioni nella profilassi antibiotica

ESC and ACC/AHA GUIDELINES

Patients

Recommendations: prophylaxis	Class[a]	Level[b]
Antibiotic prophylaxis should only be considered for patients at highest risk of IE 1. Patients with a prosthetic valve or a prosthetic material used for cardiac valve repair 2. Patients with previous IE 3. Patients with congenital heart disease a. cyanotic congenital heart disease, without surgical repair, or with residual defects, palliative shunts or conduits b. congenital heart disease with complete repair with prosthetic material whether placed by surgery or by percutaneous technique, up to 6 months after the procedure c. when a residual defect persists at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique	IIa	C

Procedure

Recommendations: prophylaxis	Class[a]	Level[b]
A - Dental procedures: **Antibiotic prophylaxis should only be considered for** dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa	IIa	C

Drug

		Single dose 30–60 minutes before procedure	
Situation	**Antibiotic**	**Adults**	**Children**
No allergy to penicillin or ampicillin	Amoxicillin or ampicillin*	2 g p.o. or i.v.	50 mg/kg p.o. or i.v.
Allergy to penicillin or ampicillin	Clindamycin	600 mg p.o. or i.v.	20 mg/kg p.o. or i.v.

Procedure che necessitano di profilassi antibiotica

- Cure dentali
- Procedure respiratorie: broncoscopia, chirurgia

  Antibiotici per os 1-2 ore prima

- Procedure genitourinarie
- Chirurgia gastrointestinale

  Antibiotici ev/os entro 30 min dalla procedura

Caso clinico: anamnesi patologica remota

- Donna, 71 anni
- 1985: protesi meccanica mitrale
- 1991: emicolectomia dx per k colon
- 1997: PM monocamerale per FA a bassa risposta ventricolare
- Novembre 2009: PM bicamerale
- Cardiopatia dilatativa (FE: 40%)

Anamnesi patologica prossima

- **2/1/2010:** febbre (TC: 38C), continuo-remittente, dolore e flogosi a livello della tasca del pacemaker
- Ricovero in UTIC:
- E.O: secrezione purulenta*, calor, rubor e dolor* a livello tasca pacemaker
- TC: 38C; PA: 120/80mmHg; FC: 76bpm; FR18/min
- VES: 50 PCR: 8 (vn<0.5)
- GB: 17000/mm3 (N% 85%)

- Tamponi ferita chirurgica: negativi
- Emocolture (6/6): POSITIVE per *Staphylococcus epidermidis*
- Ecocardiogramma TT: negativo
- Rx torace in 2 proiezioni: “..aia cardiaca aumentata in toto...”
- Urinocoltura: neg

Ecocardiogramma TT negativo….
Emocolture positive…
Febbre….

Ecocardiogramma TTE: “...lungo il decorso dell'elettrocatetere posizionato in apice ventricolare dx si osserva formazione isoecogena delle dimensioni di 11x8mm, con movimento sincrono alle fasi del ciclo cardiaco....”

- Viene iniziata terapia con Vancomicina 1gr ogni 12 ore e Rifampicina 600 mg ev

- Dopo 72 ore la pz è apiretica (TC: 36C), VES: 30 PCR: 2 GB: 7000/mm3, riduzione della flogosi della tasca del pacemaker

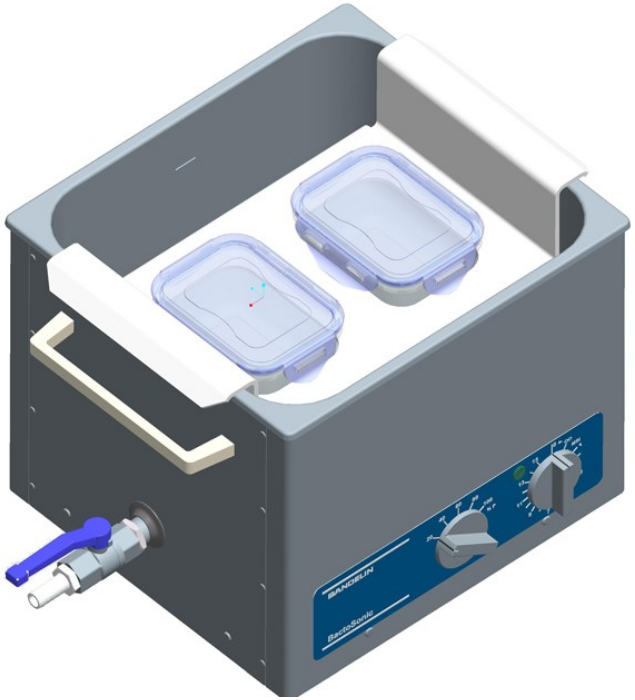
- Aumento della creatinina 4.6 mg/dl

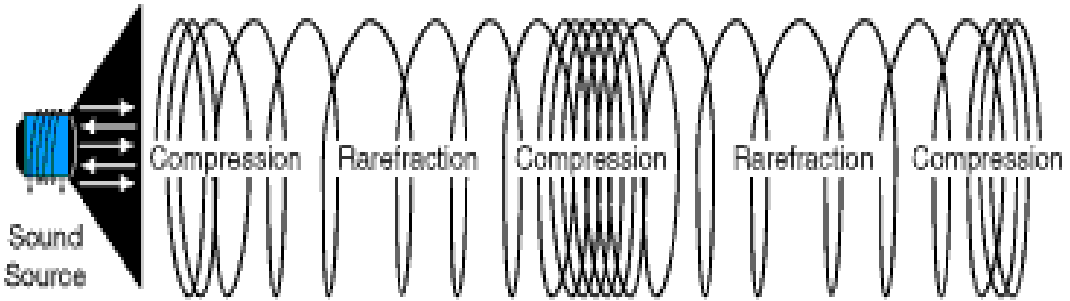
Creatinina 4.6 mg/dL: che fare?

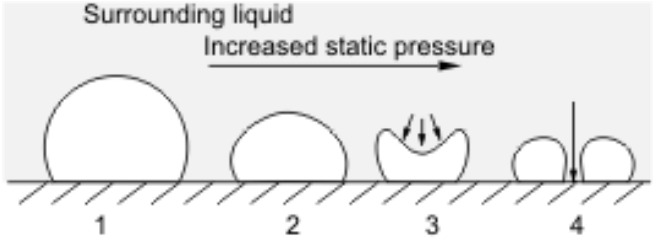
- Modificare la terapia antibiotica
- Proseguire terapia in atto
- Sospendere ogni terapia antibiotica
- Attendere e controllare altre cause di IRA

- Cambiata terapia: inizio Daptomicina 6mg/kg/die, con defervescenza, riduzione di VES e PCR, normale funzionalità renale
- Emocolture (6/6): negative
- Tampone tasca pacemaker: neg
- **15/1/2010**: Rimozione del pacemaker
- Esame colturale dell'elettrocatetere: neg
- Esame colturale elettrocatetere dopo sonicazione: *Staphylococcus epidermidis*

La sonicazione

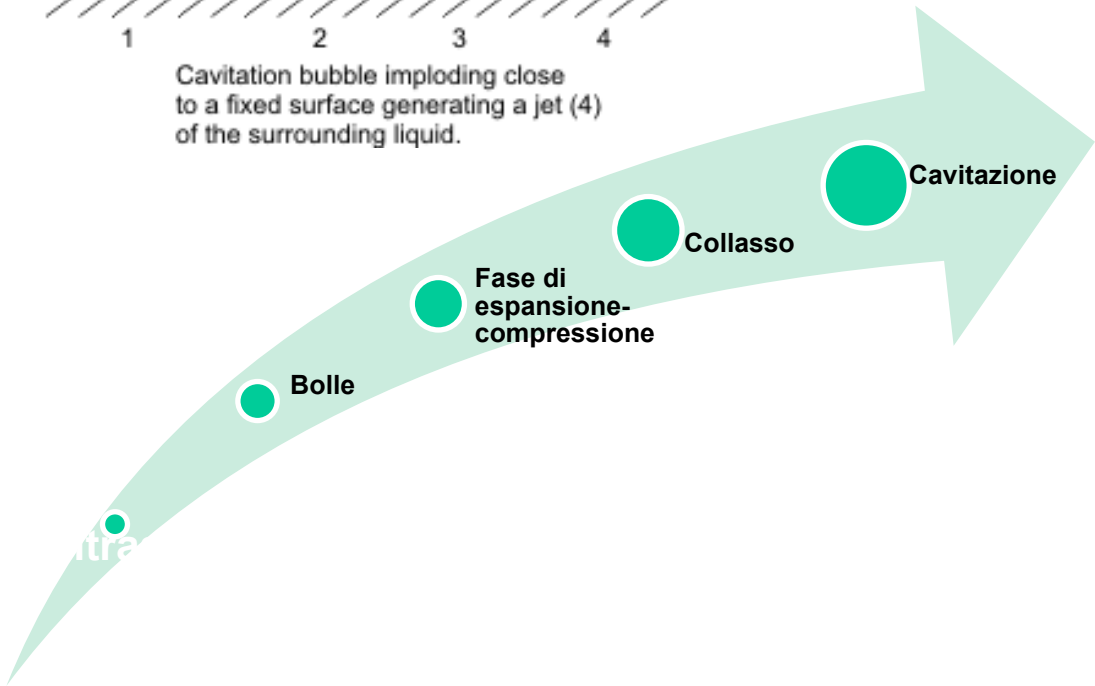






Cavitation bubble imploding close to a fixed surface generating a jet (4) of the surrounding liquid.

- **Lisi delle cellule batteriche**
- **Frammentazione del biofilm e distacco dei microrganismi**



Benzilpenicillina	R (MIC>0.5)	Vancomicina	S (MIC<0.5)
Oxacillina	R (MIC>4)	Tetraciclina	R (MIC>16)
Gentamicina	S (MIC<0.5)	Tigeciclina	S (MIC<0.12)
Levofloxacina	R (MIC>8)	Fosfomicina	R (MIC>128)
Moxifloxacina	R (MIC>8)	Rifampicina	S (MIC 0.25)
Eritromicina	I (MIC=4)	Trimetop./sulfamet.	R (MIC>320)
Clindamicina	I (MIC=1)	Mupirocina	R (MIC>8)
Teicoplanina	S (MIC<0.5)	Daptomicina	S (MIC=0.125)

- Proseguita terapia con Daptomicina 6mg/kg/die
- Normalizzazione VES, PCR, GB
- **23/1/2010**: reimpianto pacemaker (dopo 8 giorni dalla rimozione)
- Terapia proseguita per 6 settimane dopo la rimozione del pacemaker

Dispositivo medico

- **Qualsiasi strumento, apparecchio, impianto, usato da solo o in combinazione destinato dal fabbricante ad essere usato sull'uomo ai fini di:**

– **Diagnosi, prevenzione, controllo, terapia di una malattia**

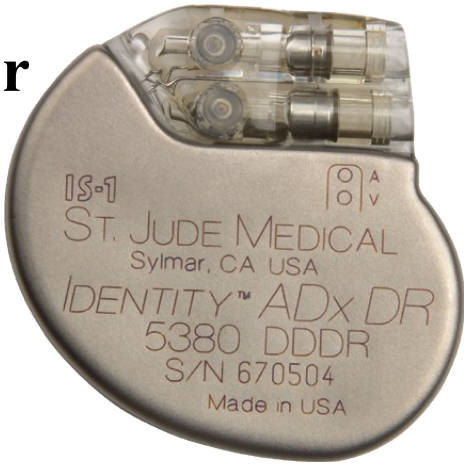
– **Diagnosi, controllo, attenuazione, compensazione di un handicap**

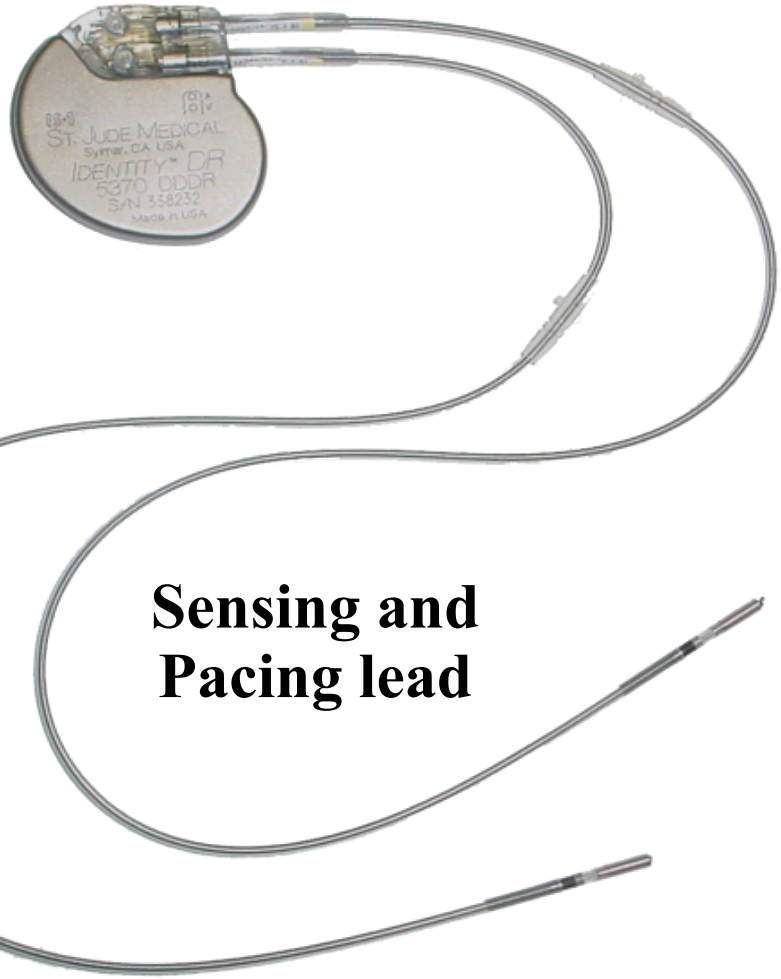
– **Studio, sostituzione o modifica dell'anatomia o di un processo fisiologico**

(Direttiva CEE 93/42)

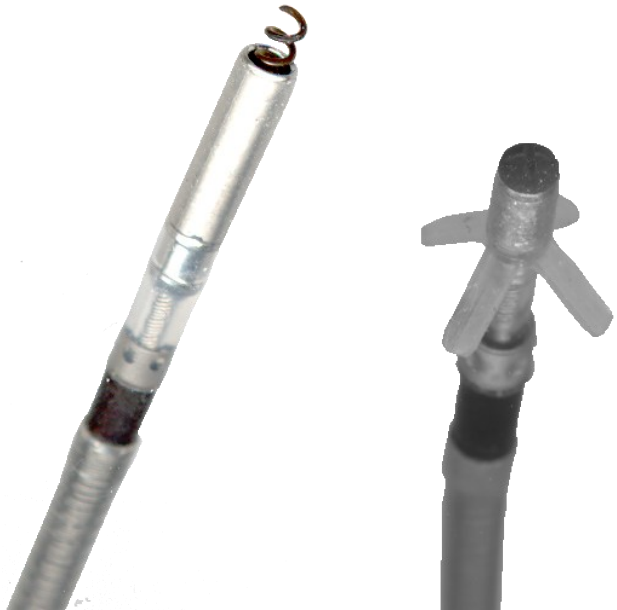
Pacing Systems

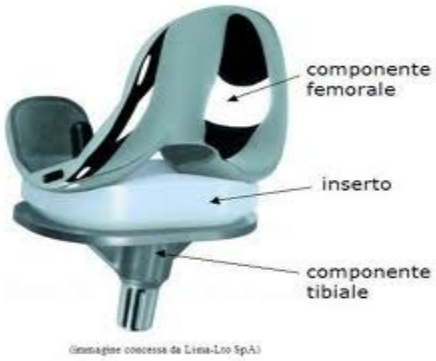
Pulse generator

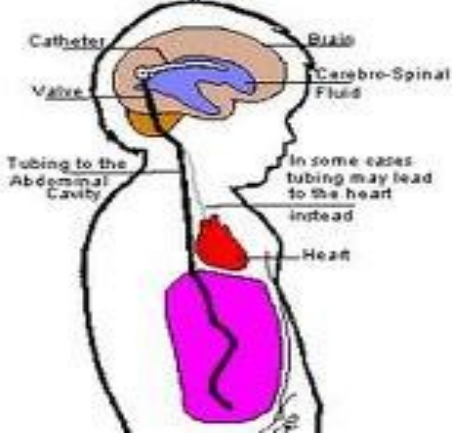




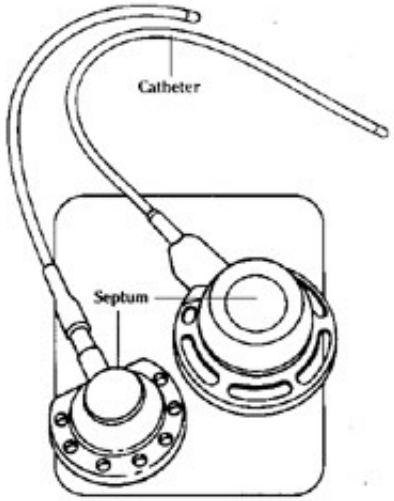
Sensing and Pacing lead

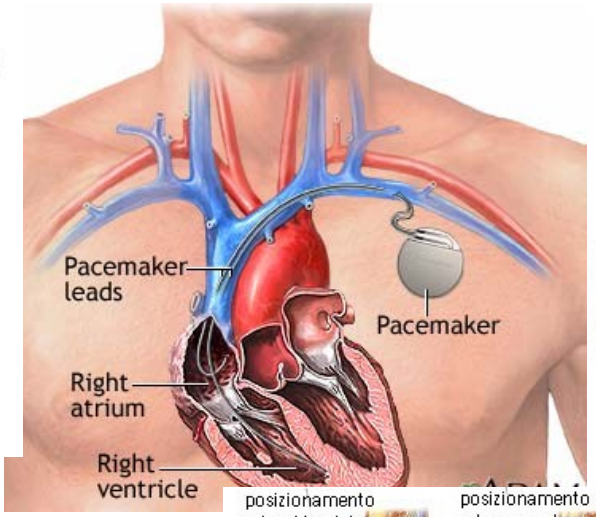


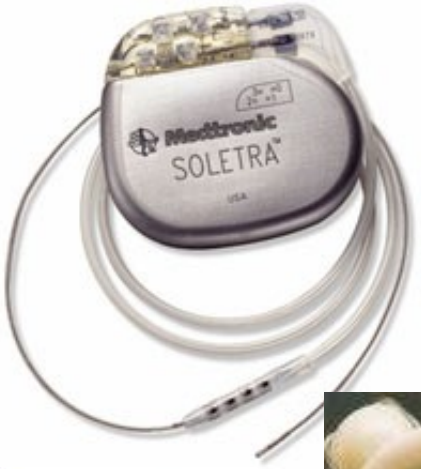


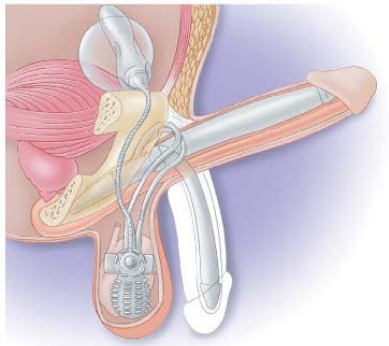


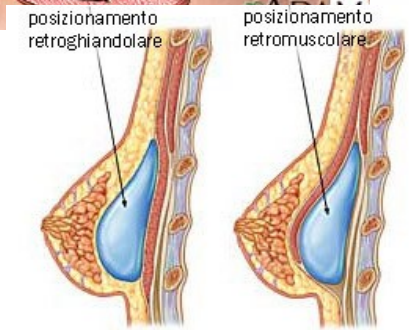
The "BiomatMan"

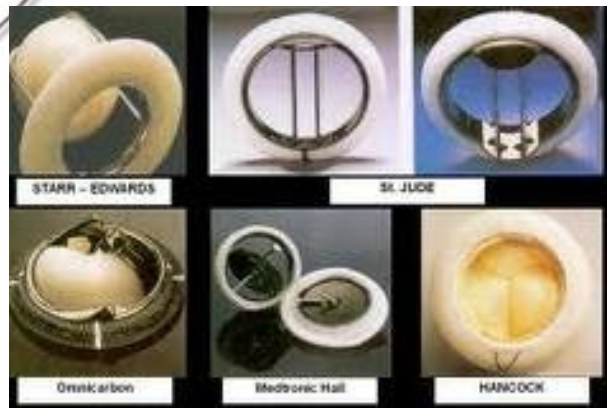








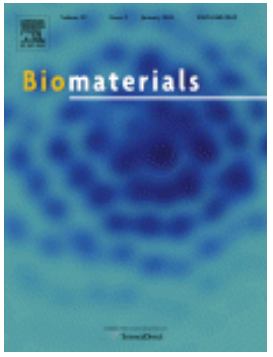




"The Biomaterials Era"

Caratteristiche ideali di un biomateriale

- Biocompatibilità
- Biostabilità
- Non interazioni con i farmaci
- Nulla o scarsa trombogenicità
- Resistenza al kinking (inginocchiamento)
- Leggerezza
- Scarsa interferenza con strumenti diagnostici
- Superficie liscia (minore adesione batterica rispetto a una superficie irregolare e/o con microfratture)



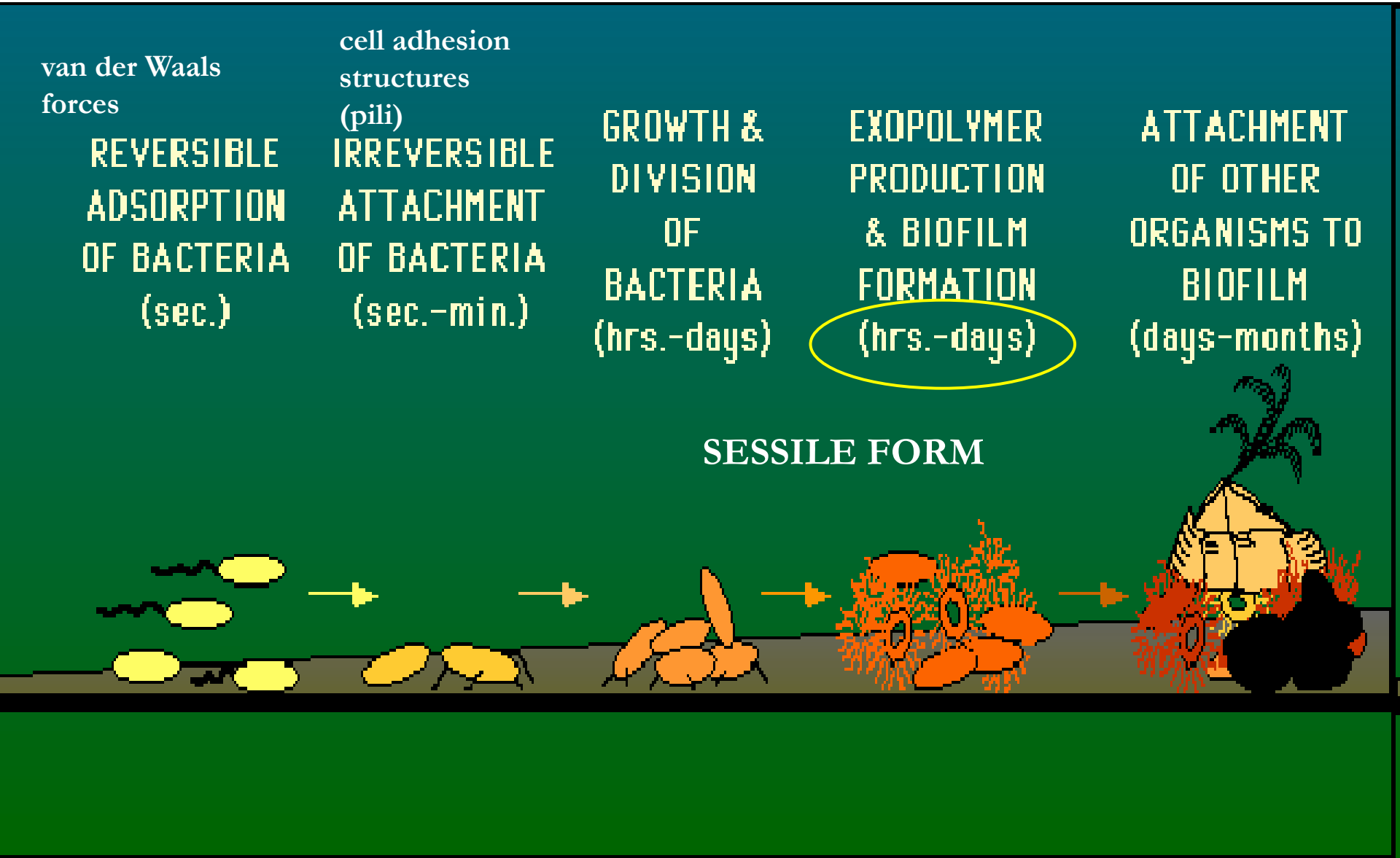
Clinical and Economic Consequences of Infections Associated with Surgical Implants

Implant	Implants Inserted in the U.S. Annually	Projected Infections of Implants Annually	Average Rate of Infection†	Preferred Practice of Surgical Replacement	Estimated Average Cost of Combined Medical and Surgical Treatment
	no.		%	*no. of stages*	*U.S. $*
Cardiovascular					
Mechanical heart valve	85,000	3,400	4	1	50,000
Vascular graft‡	450,000	16,000	4	1 or 2	40,000
Pacemaker–defibrillator	300,000	12,000	4	2	35,000§
Ventricular assist device	700	280	40	1	50,000
Orthopedic					
Joint prosthesis	600,000	12,000	2	2	30,000
Fracture-fixation device¶	2,000,000	100,000	5	1 or 2	15,000
Neurosurgical — ventricular shunt	40,000	2,400	6	2	50,000
Plastic — mammary implant (pair)	130,000	2,600	2	2	20,000
Urologic — inflatable penile implant	15,000	450	3	2	35,000

Microbial biofilms are responsible for 65% of infections in the developed world

- Bacteria commonly isolated from these devices include ***Staphylococcus aureus,*** coagulase negative ***Staphylococci, Enterococcus spp,*** and the gram-negative ***Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,*** and ***Pseudomonas aeruginosa***

Biofilm formation is a multi-step process



With an increase of cardiac devices implantation rates..

Registro italiano pacemaker e defibrillatori

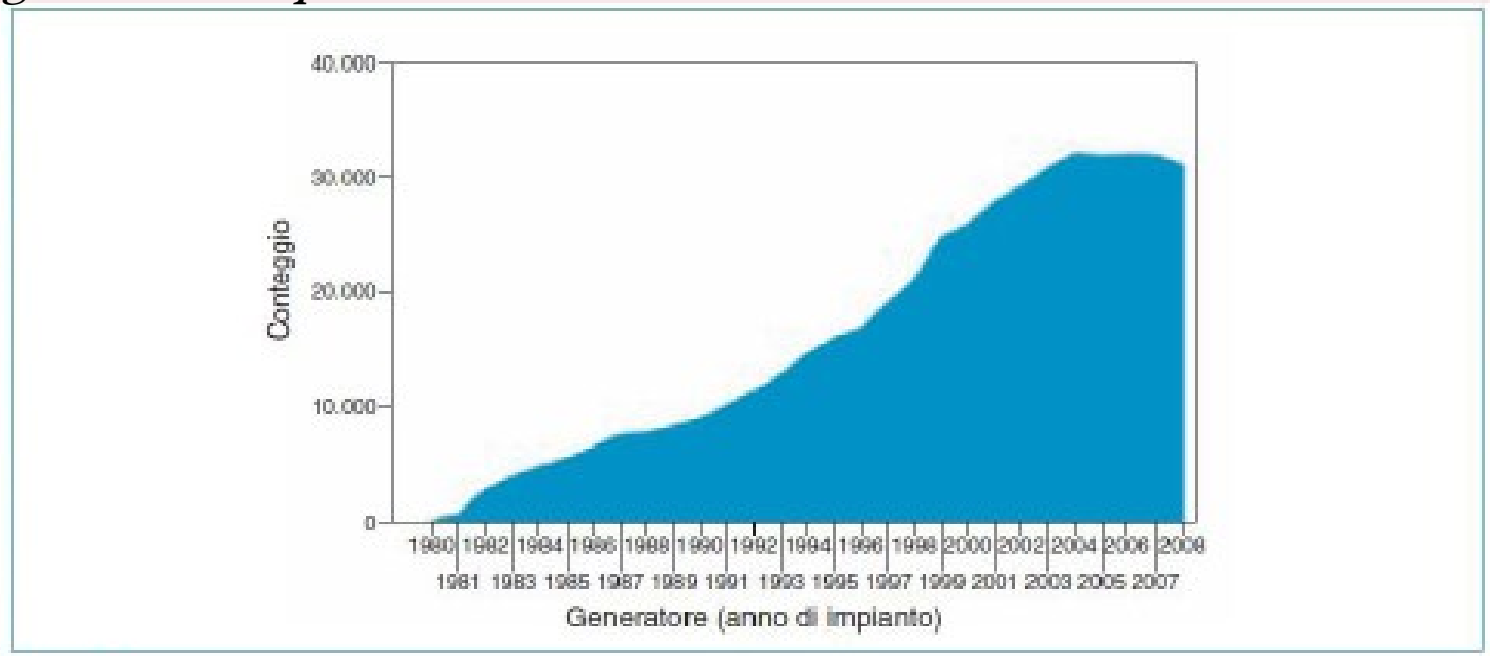


Figura 1.

Distribuzione degli impianti dal 1981 al 2008.

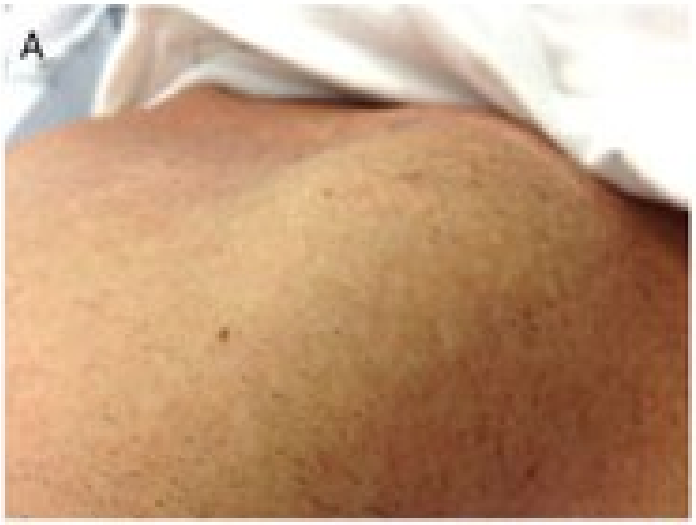
…the rate of cardiac device infections (CDIs) has been raising over the time, with a global incidence of 1.9/1000 device-years

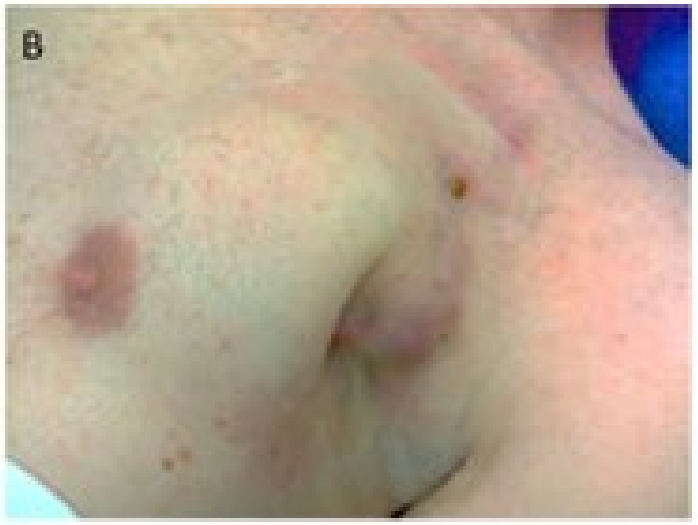
CIED infections: definizioni

- **Infezioni della tasca:**
  - coinvolgimento della tasca sottocutanea che contiene il dispositivo e/o la porzione sottocutanea dell'elettrodo

- **Infezioni profonde:**
  - Coinvolgimento della porzione endovascolare dell'elettrodo.
  - Solitamente associate a batteriemia e/o endocardite destra.
  - Possono essere associate all'infezione della tasca sottocutanea

La maggior parte delle infezioni dei device intracardiaci coinvolge la tasca; tuttavia, nel 10% dei casi è presente una endocardite device-correlata





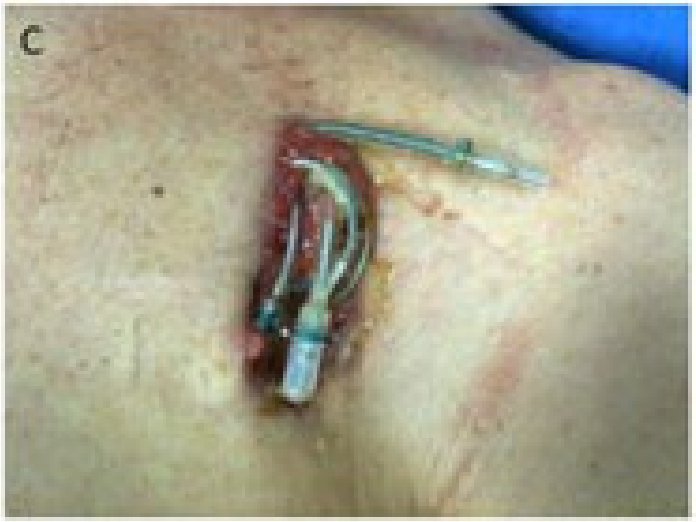
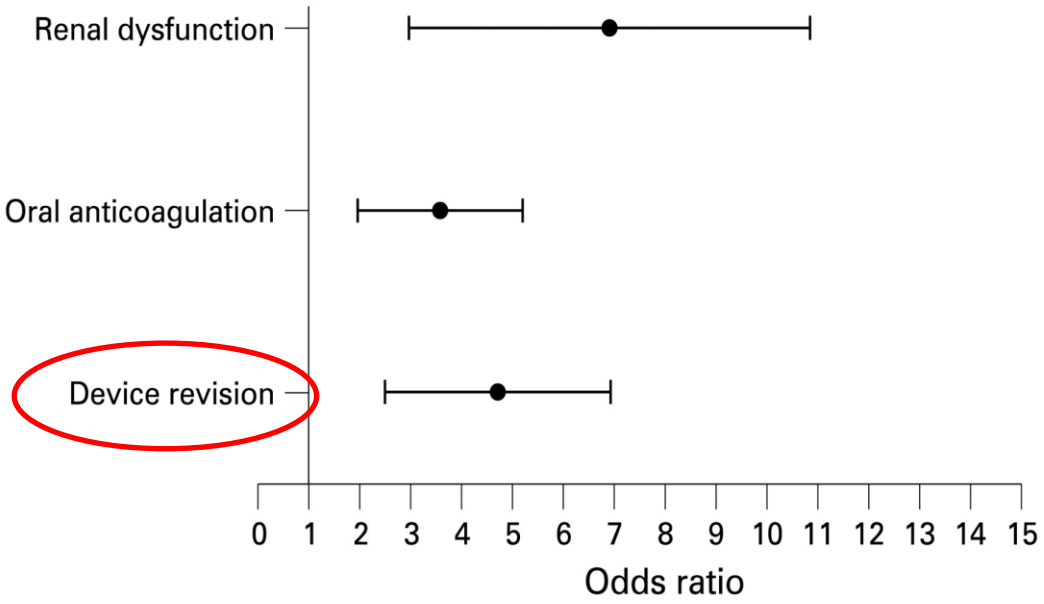


Figure 1. A: Swelling of a PM pocket. B:Skin adherence and retraction. C: Skin erosion, with exposure of PM leads. If CIED infection is possible in case A, an infective origin is surely present in cases B and C.

Risk factors and time delay associated with cardiac device infections: Leiden device registry



Device revision/replacement, renal dysfunction and oral anticoagulant use are significantly associated with the risk of CDIs

Risk factors for development of CIED infection

- **The factors associated with an increased risk of infection included:**
  - **fever within 24 hours before implantation (OR 5.83),**
  - **use of preprocedural temporary pacing (OR 2.46),**
  - **early reintervention (OR15.04)**
  - **presence of postoperative hematoma**
  - **longer procedure duration**

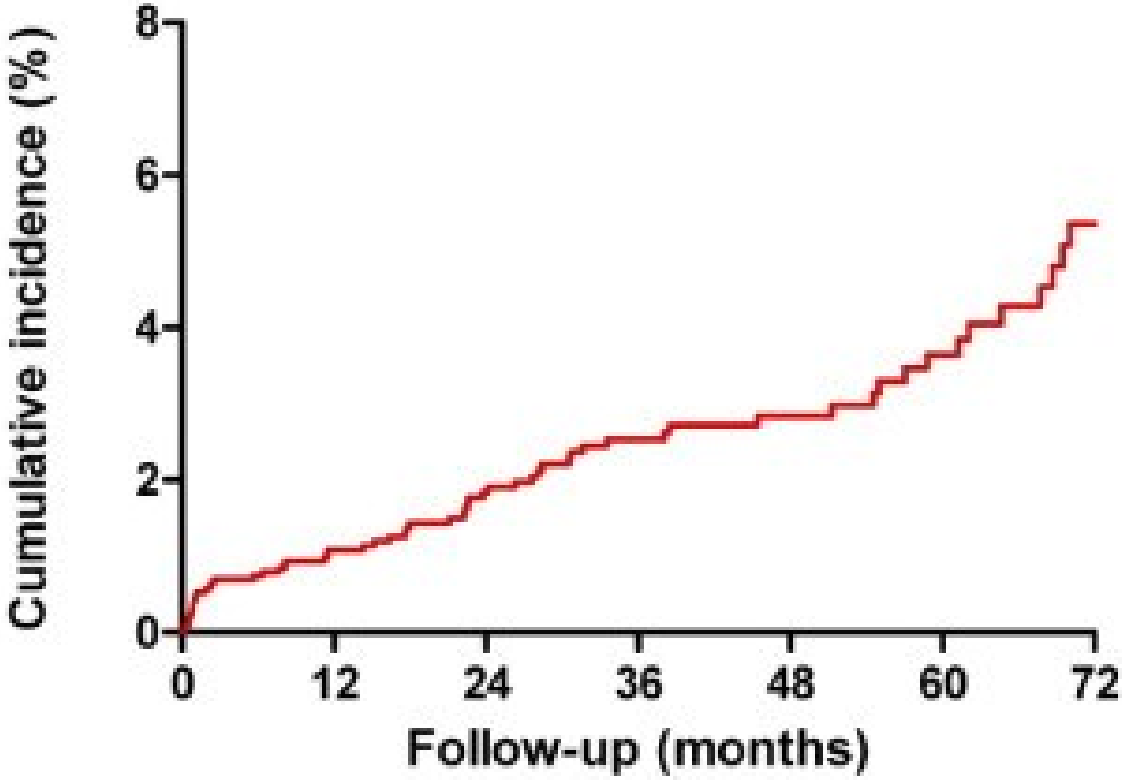
Risk factors for development of CIED infection

- **Lower risk of infection is associated with:**
  - **Implantation of a new system (OR 0.40) compared with partial or complete system replacement)**
  - **use of periprocedural antimicrobial prophylaxis (OR 0.40)**

Summary of Risk Factors

- Immunosuppression (renal dysfunction and corticosteroid use)
- Oral anticoagulation use
- Patient coexisting illnesses
- Periprocedural factors, including the failure to administer perioperative antimicrobial prophylaxis;
- Device revision/replacement;
- The amount of indwelling hardware
- Operator experience

Incidence of CDI, after initial device implantation

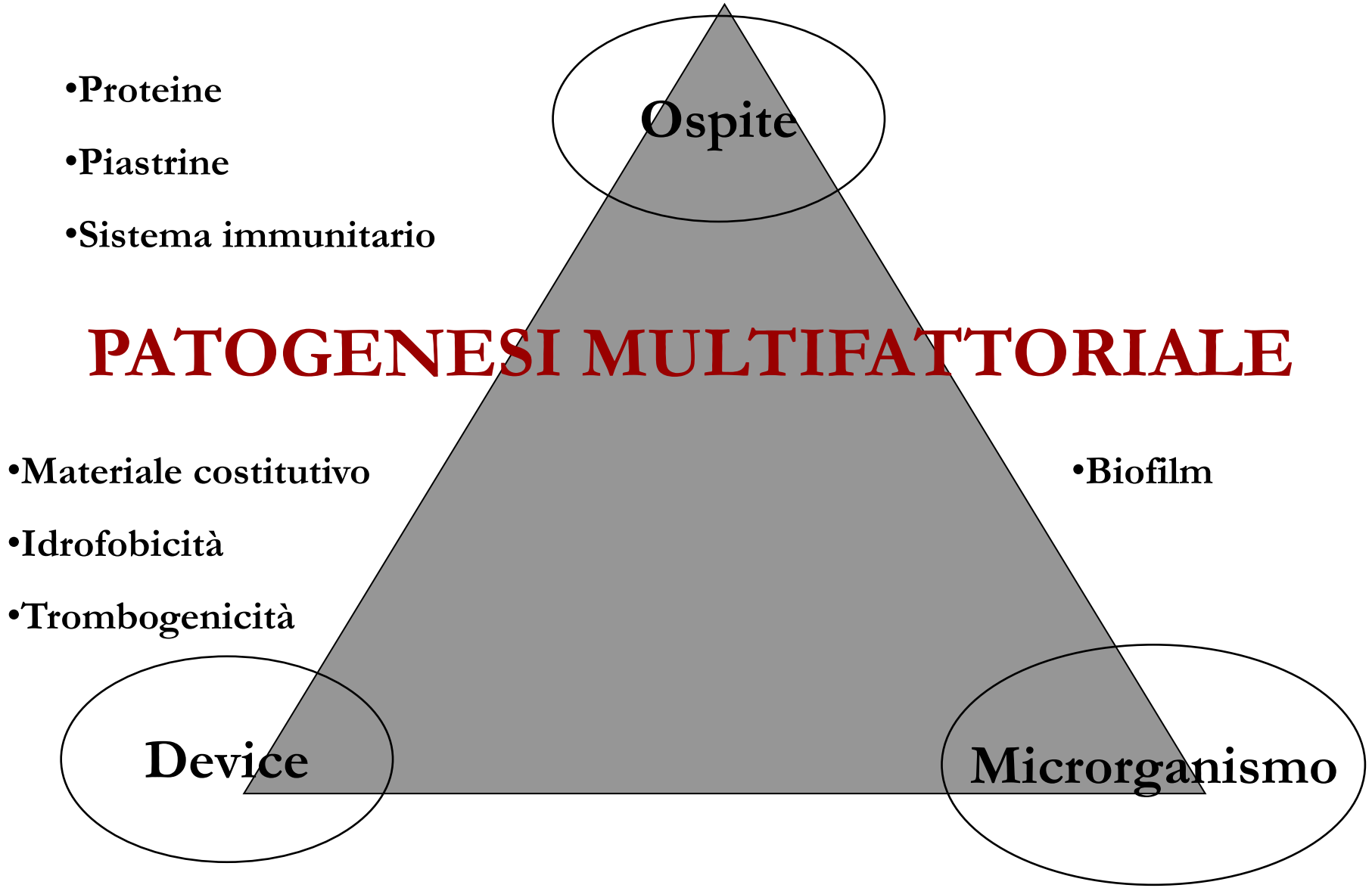


Sources for infection of the pacemaker/ICD pocket and electrode

- Contamination of the pocket at the time of device implantation: microorganisms from the pacemaker/ICD pocket can spread along the electrode to the endocardium and the electrode tip

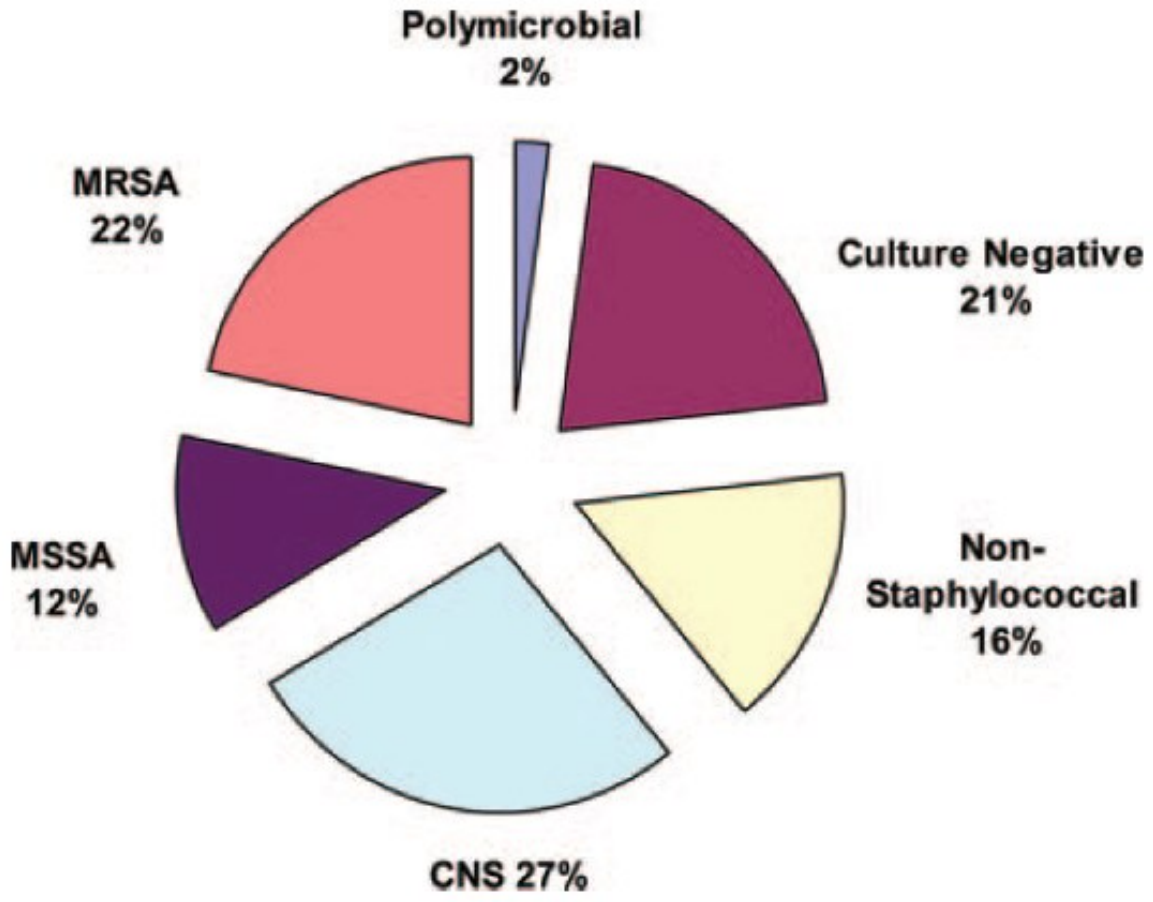
- Hematogenous seeding of the endovascular electrode during transient bacteremia related to a pacemaker/ICD pocket infection or to an unrelated site of infection

Cardiac device infection is the results of interaction between the device, the microorganism and the host



Microbiology

Staphylococcal species account for 60-70% of CDIs…..



Viola, Circulation 2010

…..howewer, 21% of CDIs are culture negative

Bacterial Colonization and Infection of Electrophysiological Cardiac Devices Detected With Sonication and Swab Culture

Martin Rohacek, MD*; Maja Weisser, MD*; Richard Kobza, MD; Andreas W. Schoenenberger, MD; Gaby E. Pfyffer, PhD; Reno Frei, MD; Paul Erne, MD; Andrej Trampuz, MD

"Sonication of the device before culture represents a more sensitive technique to detect microrganisms in device-related infections"

Circulation, 2010

CDIs: diagnosi microbiologica

- **Emocoltura: positiva in caso di endocardite**
- **Tampone della tasca: sensibilità del 31%**

(Chua, 2005)

- **Esame colturale tessuto tasca: sensibilità del 69%**

(Chua, 2005)

Sonicazione del dispositivo

Role of sonication in device related infections diagnosis

The sonication is the most suitable method in order to dislodge microrganisms in sessile phase from the biofilm on foreign body

Sonication of Explanted Cardiac Implants Improves Microbial Detection in Cardiac Device Infections

Alessandra Oliva,[a] Bich Lien Nguyen,[b] Maria T. Mascellino,[a] Alessandra D'Abramo,[a] Marco Iannetta,[a] Antonio Ciccaglioni,[b] Vincenzo Vullo,[a] Claudio M. Mastroianni[a,c]

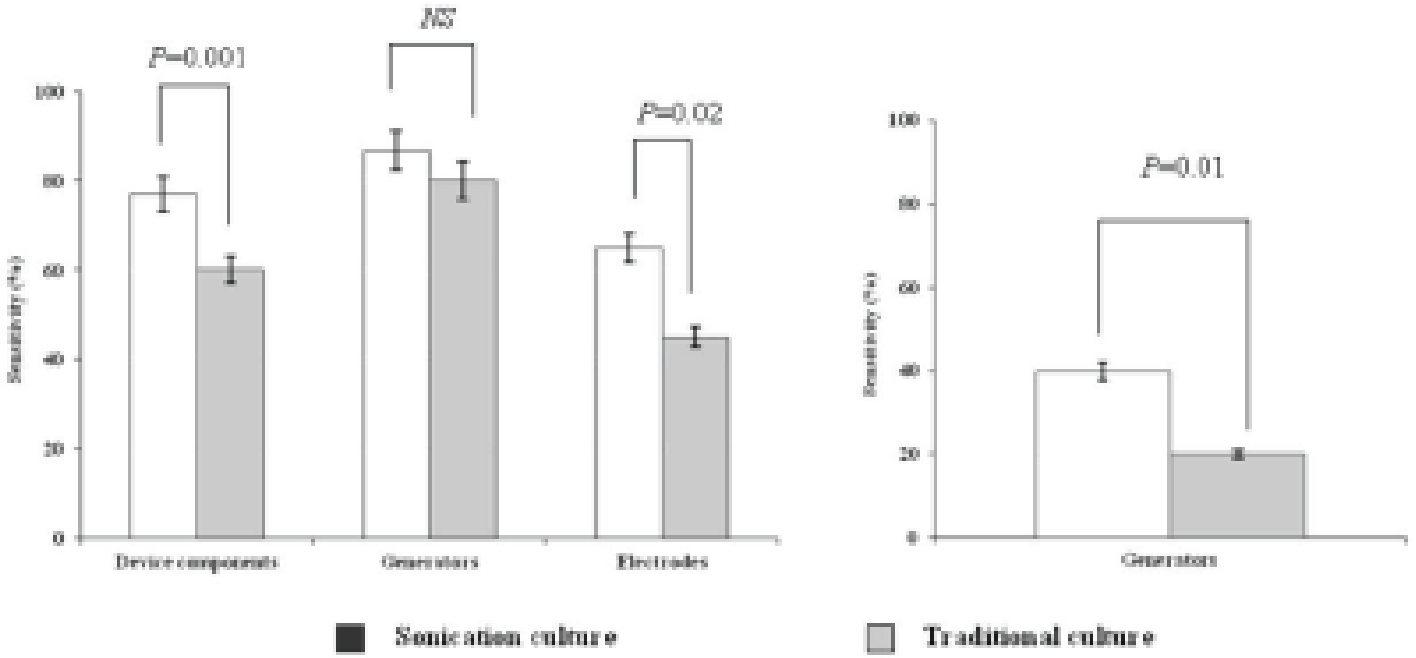


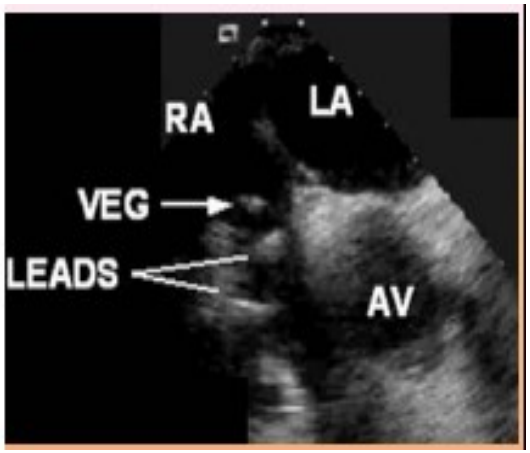
Fig. 1. Sensitivity of sonication and traditional culture for microbial detection in device components removed from infected (A) and uninfected (B) patients. Electrodes include atrial and ventricular electrodes. Value are expressed as percentage. NS= not significant.

Il ruolo dell'ecocardiogramma

In caso di endocardite associata al dispositivo, le vegetazioni possono trovarsi lungo tutto il decorso dell'elettrodo (lead endocarditis) e/o in corrispondenza della valvola cardiaca (valvular endocarditis)

TABLE 4. **Echocardiographic Findings in 44 Patients With Cardiac Device–Related Infective Endocarditis**[a]

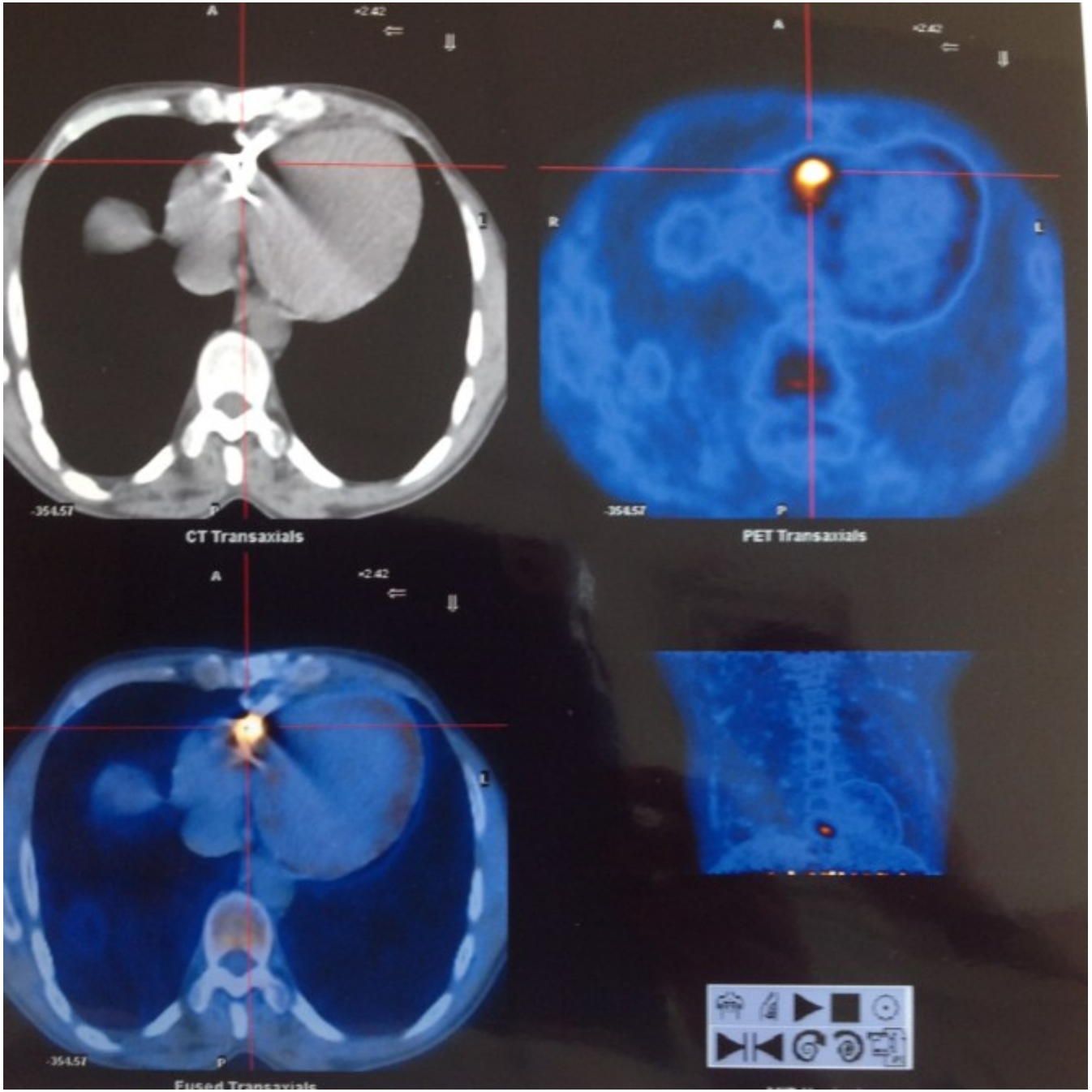
Variable	No. (%)
Location of vegetation	
Electrode lead only	26 (59)
Cardiac valve leaflet only	6 (14)
Both (electrode lead and valve leaflet)	12 (27)
Valvular involvement	
Tricuspid valve	11 (25)
Pulmonary valve	1 (2)
Mitral valve	3 (7)
Aortic valve	5 (11)
Lead vegetation revealed	
TTE	3/38 (8)[b]
TEE	35/38 (92)[b]
Valve vegetation revealed	
TTE	1/18 (6)[b]
TEE	18/18 (100)[b]
Electrode lead thrombus	5 (11)
Myocardial abscess	1 (2)



visualize by other methods. TEE examination is critical among patients with *S aureus* bacteremia, because the rate of endocarditis is significant.[67] Several prognostic features may

Il ruolo dell'ecocardiografia

- Ecocardio TT minore sensibilità rispetto al TE, sopratutto se elevata impedenza acustica e valvole protesiche
- TTE evidenzia meglio gli elettrocateteri, VCS, valvola tricuspide
- TTE indicato nelle infezioni da *S. aureus* (identifica meglio gli ascessi)
- Tuttavia, l'assenza di vegetazioni al TTE non esclude con certezza l'infezione degli elettrocateteri


CT Transaxials
PET Transaxials
Fused Transaxials

General management of CDIs

Efficacy of Antibiotic Prophylaxis Before the Implantation of Pacemakers and Cardioverter-Defibrillators

Results of a Large, Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial

Julio Cesar de Oliveira, MD; Martino Martinelli, MD; Silvana Angelina D'Orio Nishioka, PhD; Tânia Varejão, PhD; David Uipe, MD; Anisio Alexandre Andrade Pedrosa, PhD; Roberto Costa, MD and Stephan B. Danik, MD

Antibiotic prophylaxis significantly reduces infectious complications in patients undergoing implantation of pacemakers or cardioverter-defibrillators

Recommendations for antimicrobial prophylaxis at the time of CIED placement

- Prophylaxis with an antibiotic that has *in vitro* activity against staphylococci should be administered.
- If cefazolin is selected for use, then it should be administered intravenously within 1 hour before incision;
- if vancomycin is given, then it should be administered intravenously within 2 hours before incision.

General treatment issues for CIDs

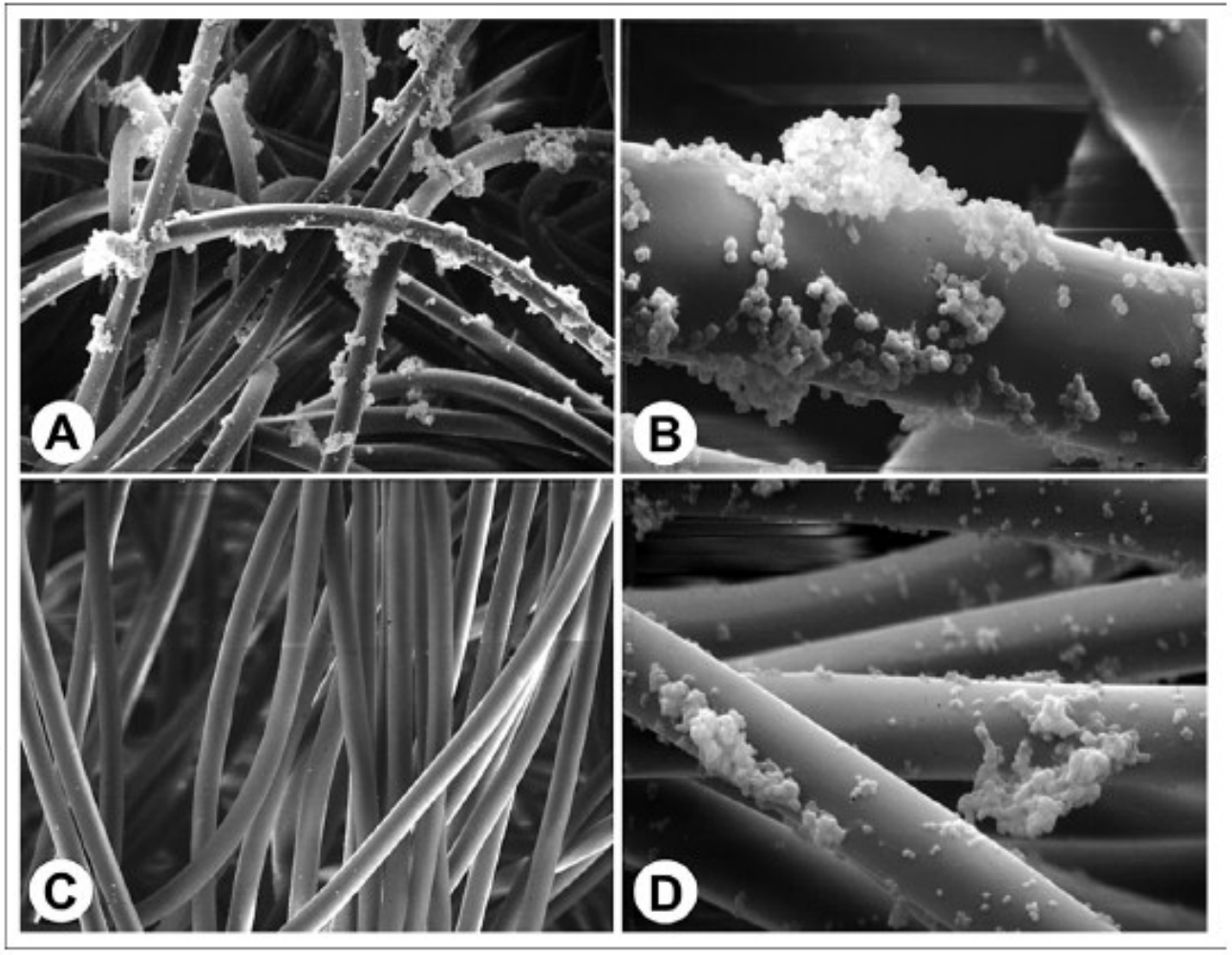
- Antibiotics: Because of the high incidence of methicillin resistance with *S. aureus and S. epidermidis*, **initial empiric therapy with anti MRSA drugs is reasonable** until susceptibility results become known

- Explantation of the device and usually the leads

- Reimplantation of a new system

Appropriate antibiotics to eradicate microbial adherence from biomedical devices

Baseline



Vancomycin treated

Daptomycin treated

Ceftriaxone treated

General management of CDIs

- **Complete removal of all hardware is the recommended treatment for patients with established cardiac device infections and should not be delayed**

- **At least 2 sets of blood cultures should be obtained from all patients with CDIs before initiation of antimicrobial therapy**

- **Lead tips cultures should be performed when device is explanted**

- **Patients with positive blood cultures should undergo transesophageal echocardiography for lead and/or valvular endocarditis detection**

Quando espiantare il pacemaker?

Per quanto tempo effettuare la terapia antibiotica?

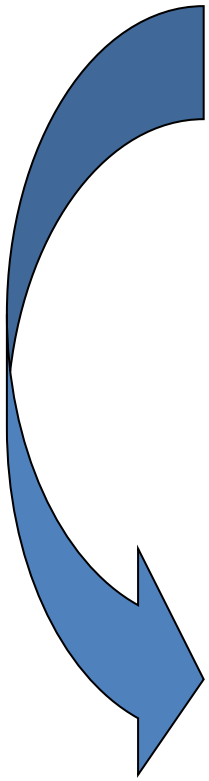
Recommendations for removal of infected CIED

- **Complete device and lead removal if:**
  - Definite CIED infection, as evidenced by valvular and/or lead endocarditis or sepsis.
  - CIED pocket infection, as evidenced by abscess formation, device erosion, skin adherence, or chronic draining sinus without clinically evident involvement of the transvenous portion of the lead system.
  - Valvular endocarditis without definite involvement of the lead(s) and/or device.

Tabella 3 - Timing dell'estrazione di un CIED infetto: vantaggi e svantaggi dei differenti approcci

	Vantaggi	*Rischi e Svantaggi*
Urgente	Eliminazione rapida del focolaio settico e del biofilm batterico	Embolia settica polmonare Complicanze post-procedurali Lungo intervallo rimozione-reimpianto Prolungato impianto di PMK provvisorio
Precoce	- Possibilità di stabilizzare il paziente - Minori rischi di embolia settica polmonare Riduzione dei tempi di degenza	Limitata efficacia della terapia antibiotica finché non viene rimosso il catetere Impianto di PMK provvisorio
Dilazionato	Possibile riduzione della dimensione delle vegetazioni Minimo rischio di embolia settica ed infezione secondaria Possibilità di reimpianto immediato (*one stage exchange*)	Prolungamento della terapia antibiotica Possibile tossicità da antibiotici Ricovero in 2 tempi Rischio di embolia polmonare a domicilio non controllata Perdita di aderenza alla terapia prescritta

There are still no clinical trial data to define the optimal duration of antimicrobial therapy for cardiac device infections



- Pocket-site infection: treat for 7-14 days after device removal

- Bloodstream infection: at least 2 weeks of therapy after device removal is recommended (up to 4 weeks if *S. aureus*)

- Complicated infection (ie,endocarditis, septic thrombophlebitis, or osteomyelitis or if bloodstream infection persists despite device removal and appropriate initial antimicrobial therapy): duration of antimicrobial therapy should be at least 4 to 6 weeks

Difficult management patients (1)

- Patients with bloodstream infection and no localizing evidence of either generator-site infection or lead or endocardial involvement

CIED removal or not?

Difficult management

- Patients with bloodstream infection and no localizing evidence of either generator-site infection or lead or endocardial involvement

- **Remove CIED if:**
  - **Occult staphylococcal bacteremia**
  - **Persistent Gram-negative bacteremia despite administration of appropriate antibiotic therapy and/or other defined focus of infection**